Aug. 31, 19

The New England Journal of Medicine

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Volume 243 SEPTEMBER 7, 1950 Number 10

RATIONAL THERAPY FOR SECONDARY AMENORRHEA*

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NEW YORK CITY

THE practitioner of medicine is often confronted with relatively young women who complain of scanty or absent menstruation and infertility. Their desire is primarily to become pregnant and secondarily to have normal menstrual periods. Yet, in the past, physicians have placed much emphasis on merely inducing menstrual bleeding, and too little attention has been directed to the problem of ovulation in these patients. It is the purpose of this communication to evaluate 50 patients treated for secondary amenorrhea in an attempt to draw certain conclusions regarding the production of ovulation and subsequent pregnancy.

A very important contribution to our understanding of menstruation in the last decade has been the work of Markee, who studied intraocular transplants of endometrium of the Rhesus monkey. Markee showed that the cyclic nature of menstruation is a result of the withdrawal of estrogen or estrogen and progesterone. He illustrated that this withdrawal has to be at a certain critical rate to produce the dehydration and regression of the endometrium that are the initial events in the vascular crisis preceding menstruation. He further clarified the pharmacology of estrogen and progesterone by showing that the effects of these two hormones on growth of the endometrium are similar though the latter is a much weaker agent in this regard. In the Rhesus monkey the menstruation was normal whether the cycle was anovulatory, which implies the elaboration and withdrawal of estrogen alone, or ovulatory, which implies elaboration and withdrawal of estrogen and progesterone. From the point of human menstruation, then, it seems that normal menstruation should always follow ovulation and normal corpus-luteum formation, or sharp withdrawal of adequate amounts of estrogen and progesterone.

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The ideal in endocrine therapy of secondary amenorrhea is to re-establish normal cyclic ovulatory menstruation without the necessity of continuous therapy. A rational approach would be to induce ovulation and thus to produce normal menses. However, at present there are no specific means to accomplish this end. One must rely on correction of metabolic and physical defects in an effort to reinstitute ovulation, and estrogen and progesterone are administered as substitution therapy to induce bleeding. There is some evidence, presented below, that such substitution therapy may have a stimulative effect on the pituitary gland or ovary or both. *It should be clearly stated, however, that simple substitution therapy in the treatment of menstrual disorders is not adequate therapy and that every effort must be made to stimulate the ovary or eradicate the factors that depress it.*

It is beyond the scope of this paper to discuss in detail the causes of amenorrhea. In general, they can be classified into four groups: anatomic defects causing obstruction; failure of the endometrium to respond to normal hormone stimulation — that is, end-organ failure; ovarian failure; and pituitary failure. There may be many contributing emotional factors that partially explain failures in function that are not often understood.

Important facts to be elicited from the history of a patient presenting herself with a complaint of absent, infrequent or scanty menstrual periods are the age and nature of onset, the duration, the appearance of masculinizing changes, recent weight changes, evidence of thyroid deficiency and symptoms of pituitary disease. Careful physical and pelvic examination should always be performed. The size of the clitoris, uterus and ovaries should be especially noted. The uterine cavity should be probed, the cervical-fundal ratio determined, a vaginal smear made, and endometrial biopsy taken if feasible. Laboratory determinations that are considered minimal are the basal metabolic rate and blood cholesterol determinations, x-ray examination of the skull and, when indicated, an intravenous pyelogram. Finally, the patient is instructed to take her rectal temperature daily be-

fore arising. *The basal body temperature record is of the utmost importance because it offers a guide to therapy, in that the appearance of a temperature curve indicative of ovulation is the end point of treatment.*

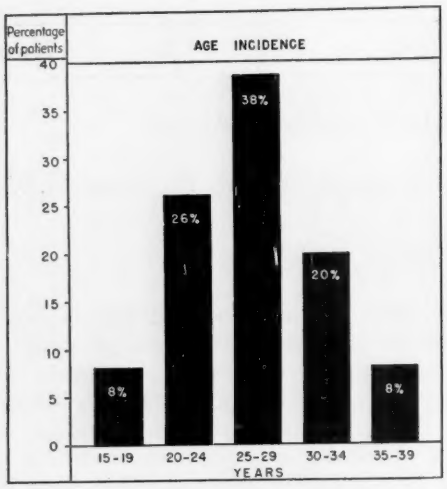

FIGURE 1. *Age Distribution of 50 Patients.*

CLINICAL STUDY

In the past two years we have treated 50 cases of secondary amenorrhea.

Age

The age distribution shows the greatest incidence in patients of twenty-five to twenty-nine years of age (Fig. 1).

Duration of Amenorrhea and Oligomenorrhea

Figure 2 compares the duration of the longest period of amenorrhea with the duration of the irregularity in menses. Whereas 44 per cent of the patients complained of a period of complete amenorrhea for four to twelve months, an equal percentage complained of infrequent periods from twelve to twenty-four months. It is to be noted that 14 per cent had a period of complete amenorrhea for over three years.

Physical Signs

Initial physical examinations revealed that 20 per cent of the patients had definite evidence of hirsutism of the face, male distribution of pubic hair or an enlarged clitoris. Eighteen per cent had definite infantile uteri in that the cervical-fundal ratio was estimated to be 1 or less. No cases of pituitary or adrenal tumor were demonstrated.

Nature of Onset

No causative factor for the amenorrhea could be discovered in 62 per cent of the patients. In these cases menstrual periods became less and less frequent and more scanty until they finally ceased altogether for at least three months. Of the remaining 38 per cent, 8 per cent of the patients experienced a sudden large weight gain immediately prior to the onset of symptoms. Twenty per cent of the patients had prolonged amenorrhea after pregnancy, and 4 per cent after a dilatation and curettage for retained products of conception. In only 1 patient could psychogenic factors definitely explain the cessation of menstruation. Sixty per cent of the patients were nulliparous; practically all desired to become pregnant.

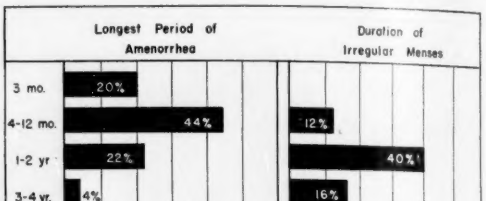

FIGURE 2. *Comparison of Duration of Longest Period of Amenorrhea and Duration of Irregular Menses.*

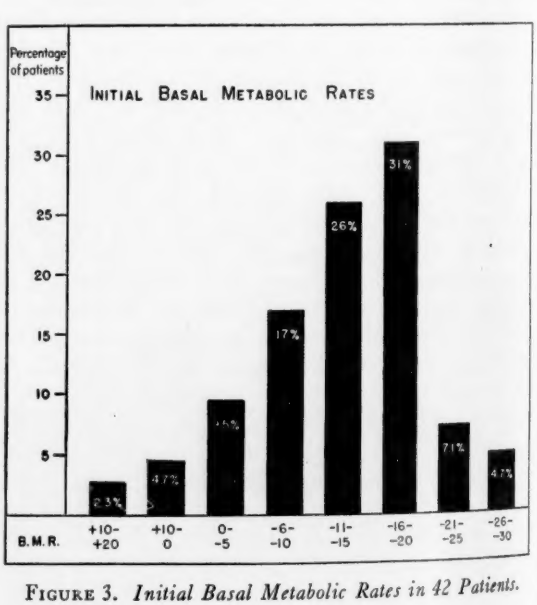

FIGURE 3. *Initial Basal Metabolic Rates in 42 Patients.*

Basal Metabolic Rates

These were measured in every case unless the rate had recently been determined by the patient's

referring physician. Figure 3 summarizes initial rates in 42 patients. It is to be noted that the largest number of patients had metabolic rates under –16 per cent. Forty per cent of the patients were definitely overweight.

Endometrial Biopsies

These were obtained frequently throughout therapy. Initial endometrial biopsies were obtained prior to therapy in 34 cases. Five patients had atrophic, 16 low proliferative, 4 hyperplastic, and 9 secretory endometrium. In many of the remaining 16 cases no tissue was obtained.

Duration of Follow-Up Study

All but 2 cases were followed for at least six months. These 2 patients became pregnant after four months of therapy and so are included. Forty per cent of the patients were followed for more than a year.

Therapy

Hormonal preparations. With the variety of hormonal preparations offered for sale, the practitioner is often confused about the value, dosage and effect of each. Furthermore, progesterone preparations are often prohibitively costly when used in adequate doses. In this study estrogen in the form of ethinyl estradiol (Eticylol)* was used. This preparation was chosen because of the almost complete lack of undesirable side effects and its relative cheapness. In an effort to find an inexpensive as well as effective form of oral progesterone, we studied and found highly satisfactory a preparation of anhydrohydroxyprogesterone (Lutocylol)* that can be administered sublingually or buccally. The tablet is small and tasteless and can be held comfortably between gum and cheek. Time of absorption varies between half an hour and an hour. Accurate chemical comparison of potency between progesterone administered in this fashion and that swallowed or taken parenterally was not made, but our clinical studies have established that anhydrohydroxyprogesterone taken buccally or sublingually is two or three times as effective as when swallowed. This increased potency is due to the fact that progesterone so absorbed is not destroyed by stomach enzymes or the liver before it reaches its site of action. By the use of this type of sublingually administered progesterone, the cost can be markedly decreased, thus obviating the major obstacle to progesterone therapy. It has been our experience that almost all disorders that are amenable to endocrine therapy can be treated with oral preparations.

Initial therapy in our series in most cases included weight reduction and administration of thyroid. Attempts were made to bring the basal metabolic rate to –8 per cent or above. If after three months no menses occurred on weight reduction and adequate replacement of thyroid, the patient was given 50 mg. of progesterone (Lutocylol) Linguets, parabuccally, daily for four days. The dose is comparable to 100 to 150 mg. daily of ingested progesterone, or 20 to 25 mg. daily taken parenterally. If adequate withdrawal bleeding followed completion of a four-day course of progesterone, the same medication was repeated on the twenty-third to the twenty-sixth day of the subsequent cycle.

If bleeding did not occur after two four-day courses of progesterone therapy, at monthly intervals, estrogen in the form of ethinyl estradiol (Eticylol) was given, in doses of 0.02 to 0.05 mg. daily for twenty-one days, followed by four days of 50 mg. daily of the progesterone Linguets. Patients were seen regularly during the third week of the cycle, and all therapy with progesterone or estrogen and progesterone was discontinued if the basal body temperature chart showed evidence of ovulation at this time.

Results

To date, every patient has been made to bleed. One patient bled after weight reduction of 18 pounds. Twenty per cent of the patients menstruated three to five months after thyroid therapy was initiated. In some of these cases thyroid was given empirically.

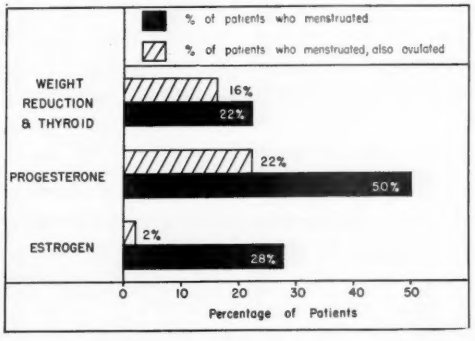

FIGURE 4. *Percentage of Patients Who Menstruated under Therapy.*

Thirty-nine patients (78 per cent) failed to menstruate after weight reduction and thyroid replacement. Of these, 25, representing 50 per cent of the patients studied, responded to a course of progesterone Linguets — that is, 50 mg. daily for four days, taken sublingually or buccally. Fourteen patients, or 28 per cent, did not respond to either thyroid or thyroid and repeated courses of progesterone, and estrogen was administered as described. All 14 eventually menstruated after the comple-

*Kindly supplied by Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey.

tion of the twenty-one-day course of estrogen and the four-day course of progesterone Linguets (Fig. 4).

A correlation between duration of amenorrhea and type of therapy required to produce bleeding was noted. In general, the longer the period of amenorrhea preceding treatment, the greater the chance that the patient needed estrogen; the shorter the period of amenorrhea, the more likely that she would respond to thyroid or progesterone (Fig. 5).

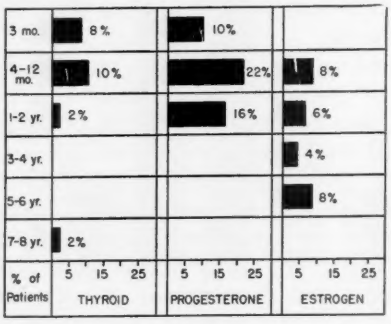

FIGURE 5. *Comparison of Type of Therapy Required to Induce Bleeding and Longest Single Period of Amenorrhea.*

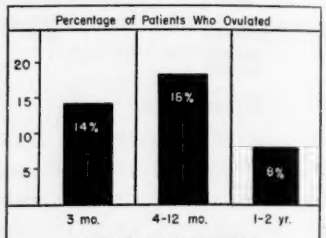

FIGURE 6. *Correlation between Occurrence of Ovulation and Duration of Amenorrhea.*

Ovulation

The basal body-temperature chart and the endometrial biopsy were used as a means of determining whether the patient had ovulated. Specifically, we considered a mid-period temperature rise and a premenstrual endometrium showing advanced secretory changes to indicate that ovulation had occurred. To date, 20 of the 50 patients studied have shown presumptive evidence of ovulation at least once during the period of follow-up study. Eight of the 11 patients who menstruated after weight reduction and administration of thyroid ovulated at least once during the period of observation. One of these patients became pregnant. Eleven of the 25 patients who required progesterone and thyroid to menstruate ovulated at least once. Four of these patients became pregnant. Only 1 patient requiring estrogen has ovulated while on therapy (Fig. 4).

A correlation between occurrence of ovulation and duration of amenorrhea was noted. Seventy-seven per cent of the patients who complained of amenorrhea of over three months' duration were noted to ovulate; 44 per cent of the patients with amenorrhea for three to twelve months, and 36 per cent of those with amenorrhea for twelve to twenty-four months ovulated. No patient with amenorrhea lasting twenty-four months or more ovulated.

Table 1 summarizes the number of ovulations observed in each patient compared with the duration of follow-up study. Ten of the 20 patients ovulated only once in a variable period. The patients with the greatest number of ovulations per six-month period were in general those who had had amenorrhea of short duration and responded to thyroid or thyroid and progesterone.

TABLE 1. *Relation of Period of Treatment to Number of Ovulations per Patient.**

Period of Treatment	No. of Patients with One Ovulation	No. of Patients with Two Ovulations	No. of Patients with Three Ovulations	No. of Patients with Four Ovulations	No. of Patients with Seven Ovulations	No. of Patients with Eight Ovulations	No. of Patients with Twelve Ovulations
mo.							
3–6	2	2	—	2	—	—	—
7–10	4	—	—	—	—	1	—
11–14	1	—	—	1	1	—	—
15–18	2	—	—	—	—	—	—
19–22	—	—	1	—	1	—	1
23–26	1	—	—	—	—	—	—
Totals	10	2	1	3	2	1	1

*Five pregnancies occurred in these 20 patients with 63 ovulations.

Spontaneous Menses after Discontinuance of Therapy

The patients who responded to thyroid alone continued to menstruate during the follow-up period, and the medication was continued. Only 5 patients of the 25 who responded to cyclic administration of progesterone continued to menstruate for four to seven months after therapy was stopped. All the

5 patients had had at least three courses of progesterone Linguets. No patient among those requiring estrogen continued to menstruate spontaneously after the medication was discontinued.

Discussion

Ovulation, spontaneous periods and pregnancy are the goals in the treatment of patients with amenorrhea. A review of the recent literature over the past eight years reveals many reports on therapy, but in many the significance and importance of ovulation has not been emphasized. Zondek,[1] Rock,[2] Cinberg,[3] Hamblen,[4] Rakoff,[5] Randall[6] and others outline various regimens of therapy with estrogen and progesterone and report success in inducing menstruation. Greenhill[7] has repeatedly stressed the point that he sees little indication to induce menstruation in a patient who does not desire children. It is obvious that if normal menstrual periods or pregnancy invariably follow ovulation in patients without organic disease, the most logical therapy would be the use of pituitary-like preparations that can stimulate the ovary directly. To date no such preparation has been shown to effect ovulation. This study, therefore, has attempted to analyze the success of other measures in effecting menstruation, ovulation and pregnancy.

No direct cause for the amenorrhea, other than hypothyroidism, was discovered in any case. The large number of cases that followed a normal pregnancy suggests pituitary or ovarian suppression or exhaustion. Those few cases following curettage for retained products of conception suggest end-organ failure due to extensive removal of the basal layer of the endometrium. All these patients gave evidence of ovulation, and yet bled only a few drops. The association of sudden weight gain with development of amenorrhea, often in the presence of a normal basal metabolic rate, was observed. The metabolism here is not well understood, but simple weight reduction often leads to spontaneous return of periods.

Of great importance was the finding of a large percentage of cases with low basal metabolic rates. The restoration of the body metabolism to normal before any other therapy is given is often rewarded with spontaneous periods. These patients have the best prognosis as concerns the possibility of ovulation and pregnancy. Once thyroid function and the weight are normal it is logical to institute *progesterone* therapy before giving estrogen for two reasons. Progesterone causes hydration and growth of the endometrium, *provided the endometrium has been primed with estrogen first.* Therefore, when bleeding follows the use of progesterone alone it is a gross measure of estrogenic activity and indicates that the prognosis is favorable. Furthermore, large doses of estrogen given over twenty-one-day cycles may inhibit ovulation if it is about to occur spontaneously. Estrogen therapy, then, should be instituted only when all else fails.

Menstruation

It is of interest that a number of patients studied in this series reported that many courses of endocrine therapy administered by other physicians had failed to produce bleeding. This failure may have been due in part to inadequate dosage of either progesterone or estrogen, failure of the physician to understand that the vascular crisis of menstruation results from the *withdrawal* of hormone support from a proliferated endometrium and failure to correct the thyroid function prior to onset of endocrine therapy. We have repeatedly noted that in marked thyroid deficiency withdrawal bleeding is more difficult, or impossible, to produce. It is our opinion that unless permanent changes have occurred in the uterus that render it incapable of responding to endocrine stimulation, every patient can be made to menstruate. We further believe that there is *definite* justification for inducing bleeding in women desiring children even if it becomes apparent that ovulation is unlikely to occur. In the first place it seems important to maintain the uterus as a functioning organ, anticipating the discovery of a potent preparation that will induce ovulation. Secondly, we have observed ovulation in patients after many months of apparently futile treatment. It has been pointed out that estrogen will probably be necessary to induce bleeding if there has been a long period of amenorrhea. This may reflect an increasing refractoriness of the uterus to stimulation as regressive changes occur, or may merely mirror the decreasing amounts of endogenous estrogen.

Ovulation

It may well be asked if the observed ovulations and pregnancies were not the result of chance rather than therapy. It is recognized that some women who menstruate only once or twice a year ovulate and conceive nevertheless. It was noted that, in treated patients, the frequency of ovulation was greatest when the preceding period of amenorrhea was short. No patient whose amenorrhea persisted over two years was observed to ovulate. Three of the 5 pregnancies occurred in the patients with amenorrhea for one or two years, the largest number of whom required progesterone to induce bleeding (Fig. 6). Certainly, from our data the factor of chance cannot be ruled out, particularly in the group with short periods of amenorrhea. It is probable, however, that in the patients who complained of amenorrhea for over one year, spontaneous periods and ovulation would have not occurred without therapy. There is some indication that cyclic administration of progesterone has a stimulative effect on ovulation in the subsequent cycle if it is considered that almost 50 per cent of

patients who responded to progesterone, but not to thyroid, ovulated. Further follow-up study will be of value in permitting definite conclusions in this regard.

Regardless of the inadequacy of present-day treatment in inducing ovulation in every patient, amenorrhea should be viewed as a serious symptom that demands energetic and often prolonged treatment. Under no circumstances should a young girl be told that failure to menstruate is inconsequential and that nothing need be done about it.

Summary and Conclusions

Ovulation is the end point in the treatment of secondary amenorrhea. The basal body-temperature record of each patient should be followed closely, and therapy discontinued if ovulation is seen to occur.

Thyroid function and body weight should be restored to normal as the first step in therapy.

The cyclic use of progesterone will result in bleeding in favorable cases and at times may result in ovulation.

The failure of thyroid or progesterone to induce bleeding is an indication for estrogen therapy and suggests an unfavorable prognosis.

Fifty patients with secondary amenorrhea were treated. All were made to bleed. In 20 patients ovulation was noted one or more times. Five pregnancies occurred in this group.

The use of an effective potent anhydrohydroxyprogesterone preparation, administered sublingually or parenterally, is reported.

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PUBLIC MEDICAL CARE IN GREAT BRITAIN AND THE SCANDINAVIAN COUNTRIES*

Basic Policies

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BOSTON

PUBLIC medical care, characterized by the utilization of general tax funds for the support of medical-care programs and the use of public agencies for the administration of the tax-supported facilities and services, is in a far-advanced stage of development in Great Britain, Sweden, Norway and Denmark. The present systems are the result of long experimentation with various methods of organization and are still in process of revision. They are not finished products but do show the pattern being shaped in "the workshop in which the future is being made" in these countries.

In Great Britain, a comprehensive program of public medical care for all the people, based on the National Health Service Act of 1946, has superseded the limited compulsory health insurance scheme for selected socioeconomic groups. In Sweden public medical care is predominant, subsidized voluntary sickness insurance playing a minor role. It will be expanded, and subsidized voluntary insurance for medical care will be discontinued in favor of a limited program of compulsory insurance when legislation approved in 1947 comes into force. In Norway and Denmark large-scale systems of public medical care are operating in functional co-ordination with administratively separated compulsory sickness insurance programs of broad scope, and they are likely to be extended.

Although public policy in these countries has tended to favor the use of general tax funds for the support of essential facilities and services for the sick, it has, as a corollary, shown a tendency to rely less and less on the method of insurance for the purpose of raising *all* the funds required for the operation of comprehensive medical-care programs. On the other hand, all four countries have given preference to the principle of insurance in financing the provision of cash benefits, such as those designed to compensate persons for loss of income in case of disabling sickness or injury or during certain periods prior to and after delivery.

At different rates of speed Great Britain, Sweden, Norway and Denmark have been moving toward the same goal: the establishment of nation-wide systems of comprehensive medical care for everybody. Without qualifications the people in these countries endorse not only this objective but also the principles of national responsibility and of governmental action for its attainment. They are motivated by the conviction that initiation and improvement of medical-care programs for

*The four countries were visited in the fall of 1949 on a travel grant from the Rockefeller Foundation.

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all is one of the many steps necessary to assure equal opportunity for everybody to live a personally satisfying and socially useful life, to construct societies where men will be both free and happy and, ultimately, to attain social as well as political democracy.

Nonpartisan Approach

The nonpartisan approach to the organization of medical care is generally accepted and strictly observed.

In Great Britain the broad policies of the National Health Service Act have been and continue to be backed by the Conservatives as well as Labor. It was the Coalition Government under Winston Churchill's leadership that accepted the proposal of a comprehensive service in 1944, and it was the Labor Government that two years later enacted it with only one important change in policy — namely, the nationalization of hospitals. Mr. Churchill, speaking for his party as well as himself, in 1943 went on record as favoring both the establishment of a national health service "on broad and solid foundations" and the development of "national compulsory insurance for all classes, for all purposes, from the cradle to the grave."

In Sweden the leaders of the conservative party much like the Social Democrats have repeatedly stated their firm belief in public medical care for everybody as an integral part of a broad system of social security. The convictions of all major parties have found expression in the law of 1947, designed to reorganize, extend and improve the existing provisions for medical care, and in other recent laws introducing important changes in and additions to the system of social insurance.

In Norway, in 1945, all political parties issued a joint programmatic declaration calling for a "universal social security system covering sickness, disability, unemployment, and old age," and, in 1948, detailed proposals for the revision of the medical-care program were submitted to the Storting (Parliament).

In all four countries there are disputes about the best method of attaining the end desired by all, and especially about technical details and administrative organization, but the conflicting views are examined and discussed objectively and in a spirit best described by the frequently heard statement: "We endorse the principle of comprehensive service for everybody and want to make such a program work."

Methods of Organization

In all four countries the provisions for medical care in the widest sense of the term are part and parcel of broad programs of social security already in operation or in process of development. They differ in organization and administration but are always linked to social insurance schemes assuring minimum protection against such hazards as temporary disability due to sickness, accident or maternity; long-term disability and invalidism due to sickness or accident; death of the breadwinner; old age; and unemployment. The social insurance schemes in Sweden, Norway and Denmark include programs providing for certain types of medical care and complementing the services maintained by public agencies out of general tax funds. In contrast, the British National Insurance system excludes medical care, which is furnished through the National Health Service. Public assistance programs for persons depending entirely on public support and a variety of special social services round out the social-security provisions in all four countries.

Great Britain

The British system, which came into operation on July 5, 1948, shows the basic characteristics of public medical care and not of compulsory sickness insurance. Eligibility to the National Health Service is extended to any resident regardless of citizenship or income and also to transient foreigners. The program covers the services of physicians, both general practitioners and specialists, of dentists and of public-health nurses ("health visitors"), visiting nurses ("home nurses") and nurse-midwives; hospitalization in general and special hospitals of any type, including ambulance service; prescribed medicines and drugs; and prescribed appliances of any type.

Administrative responsibility is vested in central, regional and local agencies. At the central level it rests with the Minister of Health in England and Wales and the Secretary of State in Scotland. Regional boards are acting as agents of the national agencies for the organization, development and general administration of hospitals and specialist services within their area; they use hospital management committees for the administration of smaller or larger groups of hospitals within the regions. At the local level "Executive Councils," which are agents of the national agencies and operate under their general supervision, are in charge of the administration of the services of "family doctors," dentists, pharmacists ("chemists") and other professional and auxiliary groups. Parallel to and separated from the executive councils there are the units of self-governing local authorities, such as county and county borough councils, which are responsible for the administration of preventive health services maintained by local governments and for a variety of other services, such as ambulance service, home nursing and visiting housekeeper's service. The central, regional and local agencies are assisted by advisory committees, and the regional and local units make wide use of administrative committees, whose mem-

bers, numbering about 12,000 in 1949, serve without remuneration.

In July, 1949, at the end of the first year of operation of the National Health Service Act, about 95 per cent of the total population had registered for the Service, and nearly nine tenths of all general practitioners of medicine, more than nine tenths of all specialists, all but a small number of dentists and virtually all pharmacists were on the lists of participants.

The total cost of the program in 1949–1950 amounted to £449,171,732 and turned out to be much larger than originally estimated because of an "overwhelming volume of need" and a demand for services by far exceeding expectations. Of the total expenses £358,509,550, or about four fifths, were defrayed out of general tax funds, the National Insurance system contributing £40,500,000 or about one eleventh. The total expenditure represented less than 4 per cent of the national income and about £9 per eligible person. For 1950–1951 the total cost is estimated at £464,514,000,or close to £10 per eligible person, and the expenditure of tax funds at £392,935,000, or more than four fifths of the total. If one assumes that in 1949-1950 £1 actually bought in Great Britain what $4 bought in the United States of America, the total average cost of the British National Health Service in that year was about $36 per person. To this figure must be added the unknown but in all probability relatively small expenses made by the people not obtaining service from the official program and by public and voluntary health agencies contributing to the support of certain services out of their own resources. For the purpose of comparison it is interesting to note that the total average expenditure for medical care in the United States in 1949 amounted to about $70 per person and represented 4.9 per cent of the national income.

Sweden

Sweden is in a transition period following the adoption of a national law passed by the Riksdag on December 18, 1946, and approved by the Crown on January 3, 1947. The present Swedish system comprises a highly developed program of public medical care, the result of a slow and continuous growth over a long period, and a program of voluntary sickness insurance subsidized by the national government out of general tax funds.

The program of public medical care includes the construction and equipment of public hospitals and clinics of all types; the maintenance of these medical-care facilities, including the full-time staffs of professional and auxiliary personnel, with only nominal rates charged for hospitalization; complete dental care (in 1948 available to more than 40 per cent of the population); and the supply of drugs prescribed by physicians outside the hospitals, some drugs being furnished free of charge and others at a price 50 per cent below cost.

Authority for formulation of broad policies and general supervision is vested in the Royal Medical Board, an agency of the Ministry of Social Affairs, and the responsibility for direct administration of all services under public auspices, except a few hospitals, is given to large district organizations, the "provincial councils," and to local units of government, the county councils and the independent cities.

The voluntary sickness associations, numbering about 1600, usually provide for hospitalization and reimbursement of two thirds of the fees of physicians for office and home care and of the cost of prescribed drugs in addition to cash benefits in case of disability and maternity; in some instances they go beyond this minimum. They operate on the basis of a national law, which requires registration of all associations and provides for approval of associations wishing to participate in the national program, the payment of tax subsidies to approved organizations and their supervision by an agency of the Ministry of Social Affairs. In recent years between a fourth and a third of the total operating income of approved voluntary organizations has come from tax funds. Despite these substantial tax allocations the voluntary associations have been unable to offer more than limited services and cash benefits and to reach a satisfactory proportion of the people in the lower-income groups.

In 1947 general tax funds covered nine tenths of the combined expenditures for maintenance of tax-supported services and for subsidies to voluntary sickness insurance organizations. The total outlay amounted to S. Kr. 544,000,000, including S. Kr. 215,000,000, or about 40 per cent, borne by the national government, S. Kr. 204,000,000, or about 37 per cent, borne by county councils, S. Kr. 109,000,000, or about 20 per cent, borne by cities not belonging to county councils, and S. Kr. 16,000,000, or about 3 per cent, contributed by localities.

The new system scheduled to become effective in the early fifties will expand the program of public medical care by removing the nominal charges for hospitalization and adding more drugs to the list of those available at low cost. It will introduce compulsory insurance covering the services of physicians outside the hospitals and apply this principle to all Swedish citizens residing in the country and all registered resident aliens. In addition, compulsory disability insurance will be established for all gainfully employed persons in the age group of sixteen years and over whose annual income from wages exceeds S. Kr. 600. The administra-

tive units of the present voluntary sickness insurance association will be utilized, but their number is expected to be cut in half in order to assure efficient administration of the new program, and the management of the new administrative units will be in the hands of small committees. Voluntary associations may continue for the purpose of supplementing the official program, mainly by providing additional cash benefits in case of disability, and, if operating with the approval of the national agency in charge, may receive a tax subsidy.

Denmark

The Danish system combines and interlocks public medical care and compulsory sickness insurance, including both medical care and cash benefits in case of disability due to illness, of maternity and of death of the insured.

The extensive program of public medical care provides for the construction and equipment of all types of hospitals, clinics and related facilities owned and administered by public agencies; the support of selected types of public services, especially hospitalization, transportation to or from a physician, midwife, or hospital; radium treatment; and the supply of essential drugs, such as insulin and liver preparations.

According to the statutes governing sickness insurance every Danish subject above the age of twenty-one who is a resident or employed on a Danish ship is required to be insured with one of the approved voluntary associations operating in accordance with the standards set by the national government. Nearly nine tenths of the population are covered, and most of them are in the approved "funds." The mandatory services include attendance by a general practitioner in the office or home, the services of nurse-midwives, complete care in a local public hospital and certain expensive medicines and drugs at three fourths of cost. Optional services, actually offered by many associations, comprise specialist services outside the hospital, dental care to a varying extent, home nursing, treatment in a private hospital, convalescent home care and part of the cost of prescribed drugs and appliances.

The program is financed by regular prepayments of the persons required to be insured and by tax subsidies. Allocations from the national government to approved associations furnish about a fifth, and payments from local units of government about a fiftieth of their total income. The associations are administered by self-governing elected committees and supervised by an agency of the national government. The administrative costs of all programs average 11 to 12 per cent of the total expenses for both medical care and cash benefits.

Norway

The Norwegian system constitutes a combination of public medical care and compulsory sickness insurance, organized and operated on the principles of functional co-ordination and administrative separation.

The large-scale program of public medical care comprises the construction and equipment of all types of public hospitals, clinics and institutions for the custodial care of the sick; responsibility for the greater part of the operating cost of all hospitals, clinics and related facilities maintained by public agencies; and the supply, free of charge or at reduced price, of certain essential drugs prescribed by physicians in private practice.

The compulsory sickness insurance scheme covers about three fourths of the population. In addition to cash benefits in case of disabling sickness, maternity and death of the insured, it provides for the services of physicians in the office and home, attendance by nurse-midwives, dental care, care in a public hospital, including all professional services, ambulance service and certain special treatment methods, such as physiotherapy and radium treatment. It is administered by self-governing local organizations directed by boards of five elected members and employing full-time administrative staffs, including physicians, and it is supervised by an agency of the national government. About six tenths of the total expenses of all insurance organizations is covered by prepayments of the insured, less than a seventh by contributions of the employers of insured persons and nearly a fourth by general tax funds, primarily allocations from the national government. In 1948 the total average costs of the principal program were about N. Kr. 130 per insured, or about N. Kr. 65 per eligible person, and represented about 1.7 per cent of the national income.

The plan under consideration would improve and broaden the national insurance system and at the same time expand public medical care.

Hospital Policy

The policy followed in organizing hospital services in Great Britain, Sweden, Denmark and Norway rests on the principle of public responsibility for the building and — to a varying degree — the maintenance of all types of hospitals, outpatient departments and institutions for the custodial care of the sick. It stresses the development of integrated hospital systems and makes the services of the tax-supported hospitals available to everybody, regardless of income. In 1948 the total number of all staffed hospital beds per 1000 population was 11.6 in Sweden, 11.3 in Denmark, 10.7 in Great Britain and 8.9 in Norway. Increase of the bed capacity is planned in all four countries. The hospital systems in the three Scandinavian countries are noteworthy for the high standards of all institutions for the care of the sick and the proportionately large number of beds in chronic-disease hospitals and in various types of tuberculosis hospitals and hospital-like homes for patients with

advanced tuberculosis, the rate of beds for tuberculous patients per annual death from tuberculosis being approximately 4 in Sweden and Denmark and about 2.7 in Norway.

In all four countries public hospitals admitting patients regardless of income occupy a dominant position not only in the hospital systems but also in the medical care programs. In Great Britain all municipal and most of the nonprofit voluntary hospitals, clinics and other facilities for the care of the sick have been taken over by the national government with the initiation of the National Health Service. The transfer of nonprofit voluntary hospitals to public ownership had become inevitable, owing to their steadily mounting deficits and their "excessive independence" — a long-deplored handicap to systematic development. In Sweden almost all hospitals are owned by public authorities, primarily provincial councils, county councils and cities, and only about 5 per cent of all beds are in nongovernmental institutions, many of which are nursing or convalescent homes. Similar is the situation in Denmark and Norway, where the main responsibility for general hospitals, except university hospitals, is vested in local authorities and that for mental and tuberculosis hospitals is shared by state and local authorities. Of all beds in general hospitals in Denmark not more than about 6 per cent are in nonprofit voluntary hospitals, primarily institutions of the Roman Catholic Church, and in Norway only an insignificant proportion is in voluntary hospitals controlled by the Methodist or the Roman Catholic Church. In both countries the beds for patients with mental deviations are nearly all in governmental hospitals, nongovernmental hospitals containing less than 2 per cent of the total bed capacity in Denmark and less than 3 per cent in Norway. The beds for patients with tuberculosis in Denmark are mainly in governmental tuberculosis hospitals and homes of various types. In Norway more than four fifths of the beds in tuberculosis homes providing for custodial care and some treatment are in institutions owned by public agencies.

In contrast to Great Britain the three Scandinavian countries have long accepted and gradually implemented the principle of public responsibility for the building and maintenance of hospitals of all types. In Sweden the development dates back to legislation passed at the end of the eighteenth century, and in Denmark it started early in the nineteenth century.

Regional or district organization of hospitals, especially general hospitals, for service to all the people in the respective area, is the method employed by all four countries. Great Britain is divided into hospital regions, fourteen in England and Wales and five in Scotland. The population of these regions ranges from 1,500,000 to 3,500,000 in England and Wales and in a number of instances has proved to be too large to ensure effective administration. In Sweden each province has a main hospital of the general type with all the important clinical departments and within its area usually a number of smaller general hospitals with departments of surgery, internal medicine and radiology and occasionally also small facilities with one department only. This method of organization has its origin in legislation adopted more than one hundred and fifty years ago. Denmark bases the organization of general hospitals on counties, a principle legally introduced in 1806, and at present has in each county at least one "central hospital" of 250 to 300 beds and a varying number of hospitals with 50 to 100 beds, all closely co-operating with the main hospital. Significantly, the central hospitals contain about two thirds of all general hospital beds. In Norway the county basis will be chosen for the regional organization of general hospitals under the new plan designed to strengthen a practice already in wide use.

With the exception of the relatively few and usually small proprietary institutions the hospitals in all four countries have closed staffs and compensate all their professional personnel on the basis of fixed annual salaries for full-time work in the hospital or, in the case of certain specialists and consultants, for regular part-time service according to a definite schedule. In Great Britain this method of organization is of recent origin, in contrast to Sweden, Denmark and Norway, where it has been employed for a long time. In Sweden nearly half of all physicians in active practice are full-time members of hospital staffs. The introduction of payment for the services of staff physicians is one of the factors responsible for increase in the cost of hospital maintenance in Great Britain since the initiation of the National Health Service. With some exceptions, the salaries paid to the full-time staff members are high enough to attract and hold capable men and women.

The operating costs of all public hospitals in the four countries are met out of general tax funds that cover the difference between income from charges for specified services and all expenses including those for professional services, or in the Scandinavian countries, the excess of expenses over the income derived from payments by insurance organizations and by patients billed for certain services. The hospital income obtained from sources other than tax funds is very small in Great Britain and represents about a tenth of the actual cost of general hospital care in Sweden. It reaches a somewhat higher proportion in Denmark, where the charges for members of the insurance associations are set at half the standard rate and those for other patients are kept so low that they cover considerably less than 10 per cent of the actual cost at hospitals in Copenhagen and never more than 40 per cent at other hospitals. In Norway the sick-

ness insurance organizations pay rates representing about 50 to 70 per cent of the actual cost, and patients not protected by insurance are charged nominal rates only.

Organization of Physicians' Services

In all four countries any duly licensed physician is eligible for admission to the medical care programs, and, actually, almost all are participating. It must be borne in mind that in the Scandinavian countries public medical care is interlocked with tax-subsidized sickness insurance. As a general rule, the policies chosen for the organization of general practitioners' services differ from those governing specialist services.

General practitioners in private practice who are willing to serve in a program must register with the local administrative unit in their area and consent to observe the pertinent administrative rules. In Great Britain they are free to choose any area except those declared "over-doctored" by the "Medical Practices Committees" of the Executive Councils, and through the offer of "inducement" funds as well as advice they are encouraged to settle in areas needing additional physicians. In Copenhagen admission to insurance practice is made on the basis of 1 physician for about 2000 to 2500 persons. The participating general practitioners are available to the people who have chosen them by signing up on their lists, as in Great Britain and Denmark, or to any eligible person without prior registration, as in Norway and, occasionally, in Denmark. Under the "panel system" in Great Britain the maximum number of persons (not patients) to be accepted by 1 "family doctor" is set at 4000. Early in 1949 the average "doctor list" contained the names of 2053 persons, and according to sample studies most of the relatively small number of physicians with 4000 persons on their lists had partners or assistants.

In all four countries the general practitioners are responsible for office and home care under the medical care programs and — to a varying extent — for the performance of certain functions under such programs as maternal and child health and school health services. They refer patients to outpatient departments or hospitals for a "second opinion" or specialist services but are not permitted to attend hospitalized patients, except those in proprietary or small "cottage" hospitals. The policy of barring the general practitioner from the hospital, rather than from certain procedures in the hospital, may well result in deterioration of the standards of "extramural" medical service and jeopardize all efforts to give the general practitioner his proper place in the total program. To avert this danger emphasis is placed on participation of general practitioners in ward rounds and staff conferences, detailed reports from the hospital physicians to the family doctors on findings and treatment, including suggestions for aftercare, and continued postgraduate education of the general practitioners by the hospital physicians. The co-ordination of the work of general practitioners and specialists through group practice is contemplated in Scotland, and the development of group practice units consisting of general practitioners is planned in England and Wales.

The present methods of remunerating general practitioners in private practice for service under the medical care programs include payment of a flat rate per person on the physician's list, the prevailing method in Great Britain and Denmark; payment of a basic salary in combination with a flat rate per person on the list, used in Great Britain to some extent; and the fee-for-service method, occasionally employed in Denmark. As a general rule, additional payments are made for time spent in traveling ("mileage fees") and for certain special services, and the total amounts received from the administrative agencies constitute full payment for the services rendered to the patients. In Norway the physician bills the patient according to a controlled fee schedule and collects from him, the patient being reimbursed by his sickness insurance organization for part of the cost incurred. Discontinuation of this system in favor of a basic annual salary in combination with a flat rate per person on the list and supplementary payments according to the amount of work is recommended in the 1948 report to the Storting. The new Swedish plan proposes the remuneration of general practitioners on the basis of a fixed annual salary in conjunction with set fees for certain services.

In Sweden the full-time salary system is widely used in the rural areas, where more than 500 physicians, or about 12 per cent of all, hold appointments on this basis, and is not uncommon in cities. These physicians accept any resident of their districts and as a rule render preventive as well as curative services. In addition to basic salaries they receive fees for certain services, which, in many instances, constitute up to half their total income.

Specialists are nearly always attached to hospitals and serve either full time or part time. Specialist service outside hospitals is available only on referral from the general practitioner or the attending physician.

In Great Britain the systematic staffing of all hospitals with accepted specialists in addition to "senior hospital medical officers" is under way after completion, in the fall of 1949, of the classification of all physicians practicing as specialists at the time of the initiation of the new service. This arduous task was carried out through review and evaluation of the training and experience of applicants by regional committees of specialists enjoying high reputation, with the emphasis placed on the grading of individuals rather than positions. At present the majority of all specialists are ap-

pointed for part-time work, usually a certain number of sessions per week. In the three Scandinavian countries it has long been public policy to center specialist service in the hospital and to foster full-time appointments wherever feasible. In Sweden only the chiefs of departments are permitted to render consultant service to ambulatory patients paying directly and for this purpose are offered space in the hospital without cost.

Specialists holding full-time positions with hospitals receive annual salaries with increments and in general do not engage in outside practice. In Great Britain "merit awards" for life are made to specialists with "superior" experience, skill and reputation, involving another grading of individuals, in contrast to the Scandinavian countries, where the often relatively high salaries rise according to the positions held. Part-time specialists are usually compensated on the basis of flat rates per amount of work rather than per hour.

Summary

Public medical care, supported out of general tax funds and administered by public agencies, occupies a dominant position in the health service programs of Great Britain, Sweden, Denmark and Norway and is in process of further expansion in Sweden and Norway. In Great Britain it is an entity in itself, divorced from the National Insurance scheme, and in the three Scandinavian countries it is functionally related to administratively separated programs of tax-subsidized sickness insurance.

The nonpartisan approach to the organization of medical care is generally accepted and strictly observed, all major political parties endorsing the broad policies.

The services of the present program of medical care in Great Britain and of the new Swedish program are available to all residents, regardless of income and citizenship. In Great Britain about 95 per cent of the population have registered for participation. The Danish program covers nearly nine tenths of the population. The Norwegian program applies to approximately three fourths of the people and will be extended to the entire population if present plans materialize.

Comprehensiveness of medical care is emphasized in all four countries. This principle is embodied in the acts recently passed in Great Britain and Sweden and to a very large extent applied in Denmark and Norway on the basis of various earlier laws.

General tax funds cover about four fifths of the total expenditure of the British National Health Service, nearly nine tenths of the combined expenses of the present Swedish system comprising public medical care and state-subsidized voluntary sickness insurance, and the greater part of the combined expense for the operation of the programs of public medical care and the subsidies to the compulsory sickness insurance schemes in Denmark and Norway.

The hospital policy of all four countries is characterized by the acceptance of public responsibility and the allocation of general tax funds for the building and — to a varying degree — the maintenance of all facilities for the care of the sick; the regional organization of all public hospitals; and the emphasis on closed hospital staffs and compensation of all regular staff members on a salary basis.

Any duly licensed physician is eligible for admission to the medical-care programs, and, actually, almost all are participating. In all four countries the general practitioners are responsible for office and home care and certain preventive services but not for service in the public hospitals. The majority receive flat rates per person on their lists; the minority are compensated through a variety of methods. In Sweden the full-time salary system is in wide use, especially in rural areas. Specialists are usually attached to hospitals, serve full-time or part-time and are paid on the basis of flat rates according to the amount of work.

MASSIVE HEMATEMESIS RESULTING FROM RUPTURE OF A GASTRIC-ARTERY ANEURYSM

Report of Three Cases

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IN RECENT years there has been an increasing interest in early operation as the most satisfactory treatment of acute massive bleeding from the upper intestinal tract. As a result of improvements in anesthesia, operative technic, blood replacement and general postoperative care the mortality in certain cases is lower than that resulting from conservative supportive measures.

Various investigators have attempted to clarify the factors that influence the result and determine whether one patient will stand a better chance of survival if treated by conservative measures while another will be less likely to succumb if a surgical effort is made. As long ago as 1933, Allen and Benedict[1] reviewed all the common factors over a twenty-year period at the Massachusetts General Hospital in an endeavor to find what led to continued bleeding and death in these patients. They concluded that the age of the patient had more bearing on the question of spontaneous cessation of hemorrhage than any other single feature. Stewart and his co-workers,[2] Dunphy and Hoerr,[3] and others, on the other hand, have come to regard the rate of bleeding as most important in determining the outcome. It is of interest that Aird[4] (1949) has concluded from his material that age is paramount, and that rate of bleeding, recurrence of hematemesis and persistence of pain under treatment are other factors.

If the patients over a physiologic age of fifty are to be seriously considered as candidates for early operation, which involves a lower mortality, accuracy of preoperative diagnosis takes on added importance. A carefully taken history, often given by the family or friends of a desperately sick patient, is, of course, essential in determining the location of the bleeding. The physical examination, on the other hand, often fails to aid in localizing the actual site of hemorrhage. In a recent survey of this problem at the Massachusetts General Hospital by Welch,[5] 85 per cent of emergency x-ray studies of the upper intestine revealed the offending lesion. Duodenal or gastric ulcer, cancer and gastritis are the common findings. Esophageal varices, hiatus hernia, polyp and leiomyoma are rarer causes of bleeding. Gastric erosions, overlooked ulcer, unimpressive gastritis, and blood dyscrasias make up the remainder of the 15 per cent of lesions that are not spotted by the roentgen ray. Because in a two-year period 3 patients with acute massive hemorrhage from a cirsoid aneurysm of a major gastric vessel, 2 of whom eventually died, were observed at the Massachusetts General Hospital, we believe it expedient to call attention to this rare lesion. Such diagnoses, if not considered at the operating table, will continue to be overlooked by the surgeon.

Aneurysms of abdominal visceral vessels are not rare. The splenic and renal arteries are by far the most common sites. According to a review by Rosenthal,[6] there are 69 cases of aneurysms of the hepatic artery and 5 of the cystic artery in the literature. Laipply[7] reported 33 cases of aneurysmal dilatation of the celiac axis. Isolated cases of superior mesenteric and of gastroduodenal aneurysms are known. Occasionally, spontaneous rupture of any of these vessels has occurred extraviscerally, resulting in hemoperitoneum and death (Taylor).[8]

Aside from the dilatations of the vascular wall secondary to peptic digestion, true gastric aneurysms are either arteriosclerotic or congenital. Bianchedi[9] collected 11 cases of atheromatous widening. Most were very small and several ruptured into the stomach, causing recurrent hemorrhage. A congenital aneurysm reported by him was associated with marked varicosities of the gastric veins and achalasia of all gastric vessels, causing the entire stomach to pulsate in a most remarkable manner. Levy[10] more recently reported a case of an arteriosclerotic aneurysm measuring 5 cm. in diameter lying in the left gastric vessel near the celiac axis. Melendez and Miranda[11] noted a case — similar to those reported below — in which fatal hematemesis was due to perforation of an aneurysm of the left gastric artery into the stomach, and Heuer[12] recalled a case in which a clinically undetected defect was dramatically demonstrated at post-mortem examination.

The aneurysms in the 3 cases reported below were of the cirsoid arteriosclerotic type. One of these took origin in the left gastric artery, and in the 2 fatal cases the left gastroepiploic artery was the site of the defect. All presented intraluminal bleeding of massive degree. All patients were over the age of fifty-five, and all were men. In retrospect, preferable treatment would have been an earlier surgical attack. The delay in each case was due to hesitancy resulting from lack of explicit

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x-ray proof of the site of bleeding. Surgical exploration, with all its modern adjuncts, is still a hazardous diagnostic measure; and it is questionable whether these depleted patients can tolerate the extensive procedure, recommended by Amendola,[13] of widely opening the stomach and duodenum, irrigating with saline solution and seeking the bleeding point, or whether the blind subtotal gastrectomy advocated by Ives[14] is justifiable. However, in the elderly patient who continues to bleed from the upper intestinal tract as demonstrated by vomiting or aspiration of red blood, and in whom the usual x-ray effort, limited of necessity, reveals no gross source of hemorrhage, surgical exploration under ideal conditions is indicated.

Case Reports

Case 1. I. A. (M. G. H. 529922), a 55-year-old restaurant porter, entered the Emergency Ward complaining of painless vomiting of blood. He recalled that for many years he had been constipated, and that during the 8 months previous to entry he had noted occasional black stools. There had been some inconstant burning epigastric discomfort also during the 8-month interval. Six hours before admission, because of rather sudden onset of weakness, he retired to bed. Two hours later, he was awakened by nausea and vomited a large amount of bright-red blood with clots. He vomited again while in transit to the hospital. A review of his past history revealed that he had consumed up to ½ pint of rum per week for several years.

Figure 1. *Microscopical Cross Section of the Specimen in Case 1, Showing the Actual Bleeding Point and Replacement of Mucosa by the Recent Laminated Blood Clot Lying over the Artery.*

The arteriosclerotic branch of the left gastric vessel, lying just at the level of the base of the mucosa, measured 3 mm. in diameter. There was some reaction about the defect itself, but no evidence of "gastritis" elsewhere.

Physical examination showed a tall, angular, emaciated man. The skin was pale, dry and warm. The tongue was thick, atrophic and coated. Abdominal examination was not remarkable. Within the rectum was found a quantity of black feces.

The pulse was 80, and the blood pressure 118/85.

Examination of the blood disclosed a red-cell count of 2,750,000, with a hemoglobin of 8.0 gm. per 100 cc., and a white-cell count of 12,500. The prothrombin time was 29 seconds (normal, 22 seconds). The nonprotein nitrogen was 47 mg. per 100 cc., and the chloride 104 milliequiv. per liter. The total protein was 5.3 gm. per 100 cc.

The patient was observed for 6 days on the Medical Ward. On the 1st day two transfusions of 500 cc. of whole blood were given, and an upper gastrointestinal x-ray film was taken in the prone position without abdominal palpation. The stomach was found to be high in position. No definite lesion was seen, although there was a questionable defect in the 2nd portion of the duodenum. This appeared as a duodenal polyp, and a repeat study was requested by the roentgenologist. The patient was given 1000 cc. of blood on the 2nd hospital day, and again on the 3rd day. After this he vomited an unmeasured amount of bright-red blood, and received a 1500-cc. transfusion. The situation was considered desperate, and a repeat gastrointestinal x-ray study was undertaken on the 5th day. No filling defect was seen. The duodenum was normal, and the previously noted polyp was thought to have been a blood clot. On the morning of the 6th day he had another hematemesis, and an exploratory laparotomy was performed.

At operation the stomach and duodenum and upper 90 cm. of jejunum were found filled with blood. No external abnormality was noted, and the stomach was opened in its lower body. The pylorus and duodenum were examined. On aspiration of the upper stomach it was noted that fresh blood reaccumulated. Investigation revealed that near the midpoint of the lesser curvature, slightly on the posterior wall, a 3-mm. dark nodule was discovered. From the apex of this an open vessel was actively bleeding. There was no induration, edema or suggestion of ulceration in the area. After identification of the bleeding site, a subtotal gastrectomy and posterior Polya gastrojejunostomy anastomosis were done. The patient received 1500 cc. of whole blood and 500 cc. of plasma intravenously, and throughout the operation the blood pressure was maintained at a constant level.

Acute deep thrombophlebitis became evident on the 1st postoperative day, and bilateral interruption of the superficial femoral veins was carried out. On the 8th day there was partial dehiscence of the wound. After resuture his course was uneventful, and he was allowed to return home on the 21st postoperative day.

The pathological report was as follows:

> There is a rupture of a cirsoid aneurysm of a branch of the left gastric artery; 1 cm. from the proximal resection margin on the lesser curvature there is a conical projection rising 1 mm. above the mucosa and measuring 4 mm. in diameter. Dissection reveals the firm projection to be a blood clot lying over a defect in an artery measuring 2.5 mm. in diameter. This artery arises from the left gastric artery and takes a tortuous course through the muscularis and without diminution in caliber kinks upward through the submucosa to lie in the basal portion of the mucosa, where it is disrupted. It next turns downward, passing through the submucosa and muscularis again to gain the serosa, where it continues cephalad to be severed at the proximal resection edge. Throughout its course it is sinuous and has yellowish atheroma in its wall. The remaining branches of the gastric artery to the stomach are tortuous and arteriosclerotic, but no branch with a comparable course is seen.
>
> Microscopical examination was reported as follows:
>
> At the bleeding point the mucosa is absent, replaced by a recent laminated blood clot, which covers a large defect in an artery lying just at the level of the base of the mucosa (Fig. 1). This artery, which measures 3 mm. in diameter, is unusually large for this situation and shows arteriosclerosis with intimal thickening. The superficial

half of this vessel is absent, with the blood clot closing the defect. There is pink fibrin about the superficial part of the wall of the vessel resembling fibrinoid change of peptic ulceration, but this change does not extend to the surrounding mucosa. About the vessel there is marked acute inflammatory response, with dilated submucosal capillaries, polymorphonuclear leukocytes, lymphocytes, and eosinophils cuffing the vessels and invading the surrounding tissue, and extending to include the serosa. This gastritis is localized to the area of bleeding and the remaining mucosa is not remarkable.

CASE 2. W. M. (M. G. H. 672072), a 59-year-old truck driver, had had occasional episodes of sharp epigastric pain for the past 5 years, occurring several hours after meals and relieved by sodium bicarbonate but not by food. He had had no recent distress. Over the previous 6 months the lower back had caused him pain, and x-ray films taken elsewhere suggested tuberculosis. Aspirin had been taken daily for the relief of back pain. Twenty-four hours before admission he had an episode of sweating and weakness, followed by vomiting of 1 pint of dark-red blood with clots. He vomited red blood again while in bed at home, and two

FIGURE 2. *Gross Specimen in Case 2, Showing the Mucosa of the Greater Curvature, with the 3-mm. Defect (Life Size).*
The specimen lies on a flat, hard surface, and the very tortuous left gastroepiploic branch just beneath the mucosa is clearly seen.

subsequent hematemeses occurred before he arrived at the hospital. Shortly thereafter he passed a tarry stool. The past history revealed a "very high" blood pressure several years previously, but this was thought by his family to have improved. He had consumed 1 to 6 bottles of ale a day up to 3 years previously.

On admission to the Emergency Ward he appeared to be older than the reported age of 59. The skin was pale, cold and clammy, and although he was rational he was acutely ill. The abdomen was soft, and no areas of tenderness were found. One observer thought he felt a poorly defined mass in the right upper quadrant.

Examination of the blood showed a hemoglobin of 8.5 gm. per 100 cc. and a white-cell count of 23,500. The prothrombin time was 20 seconds (normal, 15 seconds). The nonprotein nitrogen was 78 mg., and the total protein 5.2 gm. per 100 cc.

The patient was admitted to the Medical Ward with a presumptive diagnosis of carcinoma of the stomach. He was observed for four days. The immediate shock was combated with 3000 cc. of whole blood on the 1st hospital day. On the 2nd day 1000 cc. was given, and the hemoglobin was found to be 11.5 gm. On this day a barium x-ray study in the prone position revealed a small hiatus hernia and

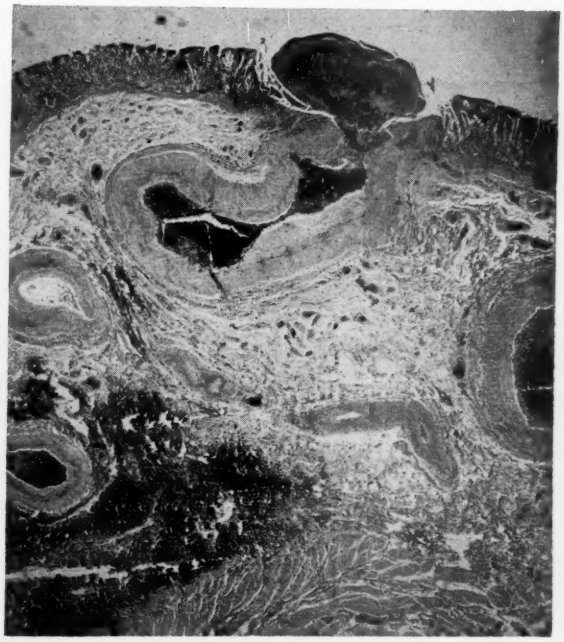

FIGURE 3. *Photomicrograph in Case 2, Showing the "Blowout" in the Large-Vessel Wall and Replacement of the Mucosa by a Thrombus, Which Also Plugs the Arterial-Wall Defect.*
The degree of intimal thickening and tortuosity of this left gastroepiploic vessel is demonstrated by the number of cross sections on this single slide. The mucosa elsewhere is normal except for the area immediately adjacent to the site of recurrent hemorrhages.

coarse rugal folds in the stomach, and the duodenal cap presented a scar with a possible ulcer crater. None of these findings were particularly striking, and exploration was postponed. Two days thereafter because of a fall in hemoglobin level in spite of repeated transfusion, laparotomy was performed.

A small pliable hiatus hernia was found. The stomach was definitely thickened, chiefly in the body, and there was a white scarred area on the first portion of the duodenum. On the presumption that hypertrophic gastritis was the probable source of bleeding, a radical subtotal gastrectomy was carried out, including the duodenal-ulcer scar. The upper segment of stomach was inspected and explored, after the proximal clamp had been removed. No active bleeding points were seen. The rugae were thickened and coarse. It was believed that the patient had bled from a diffuse gastritis. At this time, those at the operating table noted that the subserosal gastric vessels were markedly arteriosclerotic and tortuous. Twenty-five hundred cubic centimeters of blood was given, and the procedure was well tolerated.

On the 2nd postoperative day, the patient suddenly vomited 350 cc. of fresh blood. This occurred in spite of the fact that a jejunostomy tube for decompression pur-

poses had been placed in the stomach segment at the time of operation. During the succeeding 2 days he was well and took routine gastric feedings successfully. On the evening of the 5th postoperative day, however, fresh blood began to drain via the jejunostomy tube, and he vomited bright-red blood in rapid succession to a total of 2400 cc. A transfusion of 2000 cc. was given. A Miller–Abbott tube was passed into the stomach through the nares. The bag was inflated with water, and a weight attached to the nasal end of the tube. This device was believed to have checked the bleeding temporarily, and shortly thereafter the patient was taken to the operating room, where a transthoracic gastrectomy of the remaining stomach segment was done. Inasmuch as the patient was in a precarious state, no time was spent in exploring the interior of the stomach. The hiatus hernia again seemed innocuous. Note was made of the tortuous, arteriosclerotic nature of the remaining

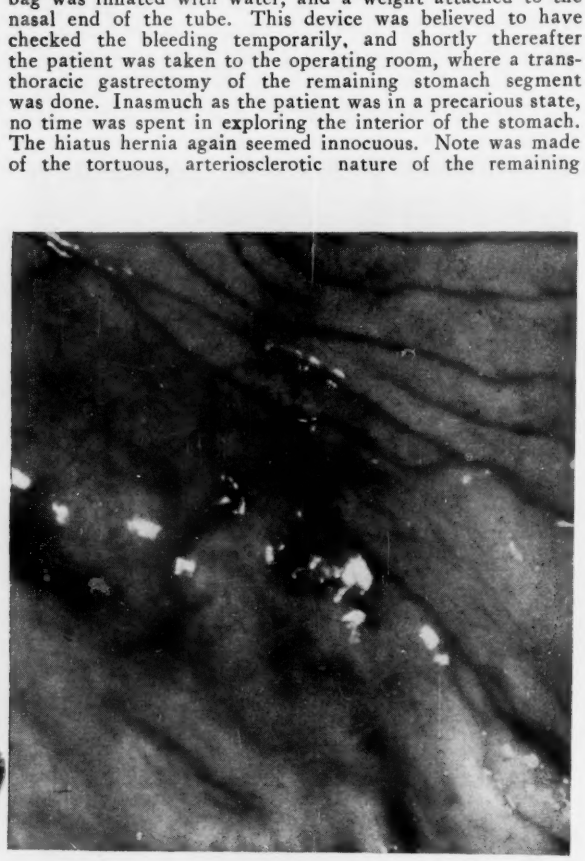

FIGURE 4. *View of the Post-Mortem Specimen in Case 3, Showing the 4-mm. Punched-Out Area Overlying the Large Tortuous Vessel, Which Is Evident in the Submucosa Beneath (Life Size).*

The mucosa elsewhere is normal.

subserosal vessels. A total of 4000 cc. of whole blood was given on this day.

For the following 36 hours the patient seemed in excellent condition, and fluids by mouth were offered. On the evening of the 2nd day, however, tachycardia, sweating and peripheral collapse gradually developed. There was some pain in the lower thoracic region, and tenderness and spasm were noted in the upper abdomen. On the following day jaundice appeared, and during the course of the day he rapidly failed and died.

Pathological examination of the first specimen revealed "chronic gastritis." Examination of the second specimen was reported as follows:

> There is a cirsoid aneurysm in a branch of the left gastroepiploic artery, with rupture and massive gastric hemorrhage, and arteriosclerosis with medical calcification in branches of the left gastroepiploic artery. All previous suture lines are intact and competent, and exhibit various degrees of healing. On the posterior aspect of the greater curvature there is a punctate, elevated area, measuring 2 by 2 mm. and raised 2 mm. above the surrounding mucosa (Fig. 2). This is covered with a cap of green-brown blood clot, which seals the orifice of a ruptured dilated sclerotic artery that lies immediately beneath. There is no scarring or inflammation of the surrounding mucosa, but palpable immediately beneath there is a tortuous sclerotic segment of a small artery, 1.8 cm. in length, which courses from the lesser-curvature side, terminating directly in the mucosal defect described (Fig. 3).
>
> At autopsy all recent suture lines were found to be intact, and stomas were patent. The duodenum, however, was markedly dilated, and its wall was discolored and, in areas, black. At one point near the site of the original duodenal-stump closure of 10 days previously, there was frank necrosis and perforation, resulting in bile peritonitis. The duodenal obstruction lay at the ligament of Treitz and just beyond at the site of the reconstructed jeju-jejunostomy, and resulted from a 180° torsion of the bowel at this fixed point.

CASE 3. A. P. H. (M. G. H. 545225), a 64-year-old man, entered the hospital in shock, and a brief history only was elicited. Evidently he had previously been in good health until 20 hours before admission, when he suddenly vomited old blood, and had several tarry stools in rapid succession. Weakness and vertigo followed, and he was brought to the hospital by ambulance. A sketchy review of his past history revealed that 7 years before he had been jaundiced, and this was thought to be due to excessive alcohol consumption. Thereafter he had stopped his heavy drinking and had been well. He had never before noted bleeding from any source.

Physical examination showed the patient to be somnolent. The respirations were slow and deep. The skin was pale and cold over the extremities, but was not moist. There was dried blood in either nostril. The pulse was 100 and strong, and the blood pressure 70/40. On examination of the abdomen no masses or tenderness was found, and neither the liver nor the spleen was felt.

Examination of the blood disclosed a red-cell count of 2,650,000, with a hemoglobin of 8.3 gm. per 100 cc., and a white-cell count of 24,600.

On the afternoon and evening of admission the patient received 1000 cc. of whole blood, and x-ray study was planned for the following day. In the morning he was somewhat less apprehensive, and the skin was warm. It was noted that there was marked edema of the eyelids. The blood pressure was constant at 120/60. However, he was shortly found to be unresponsive and lying in a large quantity of dark-red, vomited blood and tarry feces. The oropharynx was full of dark-red blood. In spite of artificial respiration, endotracheal aspiration and intracardiac administration of epinephrine, he died.

At autopsy the immediate cause of death was found to be tracheal aspiration of a large amount of blood. In the stomach 5 cm. distal to the cardioesophageal junction on the greater curvature there was a slightly raised area in the mucosa measuring 1 cm. in diameter, in the center of which there was a shallow depression measuring 4 mm. (Fig. 4). This depression was filled by a moderately firm, dark-brown thrombus, which protruded 2 mm. into the lumen of the stomach. The mucosa surrounding this depression was slightly injected, but the remainder of the gastric mucosa was normal. In the serosa opposite the shallow depression in the greater curvature a tortuous left gastroepiploic artery, which had a slight aneurysmal dilatation to 3 mm. in diameter, penetrated deeply through the layers of the stomach to lie just beneath the mucosa. The artery formed the base of the defect described. It then took a tortuous course outward through the layers of the stomach to the serosa, where three tortuous branches formed.

Microscopical examination was reported as follows:

> Sections through the slightly raised area in the fundus of the stomach show a tortuous artery in the overlying serosa. The artery penetrates through the muscularis and lies just beneath the mucosa. At one point there is a punched-out area devoid of mucosa. The base of this area is filled with an organized thrombus, which lies on the surface of the artery. The mucosa in the wall of the defect shows a moderately profuse round-cell infiltration.

SUMMARY

In view of the recent tendency to early operation in elderly patients presenting massive hematemesis, accuracy of operative diagnosis is of para-

mount importance. In this older group arteriosclerotic aneurysms of the gastric vessels can produce acute blood loss by rupture into the stomach. The actual site of perforation is tiny and is not visualized on x-ray examination. It must be considered among the differential diagnoses in any elderly patient on whom the preoperative x-ray report is inconclusive, and at operation a specific search must be made for such a lesion. Undue calcification of the external subserosal gastric vessels is usually present and should arouse suspicion.

Three cases of massive hemorrhage from internal rupture of a cirsoid aneurysm are reported. All were in elderly men in whom operation was delayed because of lack of concrete x-ray evidence of the location of bleeding. Two patients were subjected to gastrectomy; and in the sole survivor the site of rupture lay in a left gastric-artery branch and was included in the resection of the lower stomach segment.

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THE "MILK FACTOR" IN CARCINOMA OF THE HUMAN BREAST*

An Analysis of 88 Cases

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THE purpose of this study was to explore the possibility of the vertical transfer through breast feeding of an agent that might be a factor in the development of human mammary cancer. Complete bibliographic material on the subject is presented by Berner elsewhere in this issue of the *Journal*.

The difficulties of this type of study, in which the memory of the mother for an event that took place often forty or fifty years before serves as the major criterion, are fully realized. At the start of the investigation, it appeared necessary to have a control group. The possibility was considered that a statistical difference in the incidence of nursing in the two groups of patients studied would indicate whether a much larger group of cases should be studied in similar fashion, or whether it would be necessary to attack the problem from a contemporary point of view — that is, keeping records of a large group of presently newborn infants and following them into the later decades of life to determine any difference in the incidence of mammary cancer between those who were breast fed and those who were not. The data presented below indicate that neither of these projected studies is necessary.

Material and Method

Case histories of well over 1000 women with known carcinoma of the breast were made available by several hospitals.‡ The report of the pathologist who examined the tissue was accepted as confirmation of the diagnosis. From these cases were chosen 88 patients who, together with their mothers, were still living. As a control group, a similar selection was made of 86 patients who had had vaginal plastic operations performed at this hospital, and in whom no neoplastic process had been discovered from the history, physical examination or pathological examination. The average age of the two groups was the same. Explanation of this unanticipated feature seems to be that though both conditions under study usually occur in the later decades of life, only patients whose mothers were still living were included in the report.

To all these patients letters were sent explaining, so far as possible, the purpose of the study

*From the Free Hospital for Women.
Supported in part by a grant from the American Cancer Society, Massachusetts Division, Inc.

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‡I am indebted to the doctors and staffs of the Parkway, New England Deaconess, Palmer and Massachusetts General hospitals of Boston, Pondville State Hospital, Walpole, Choate Memorial Hospital, Woburn, and Cushing Veterans Administration Hospital, Framingham, Massachusetts, and Mary Imogene Bassett Hospital, of Cooperstown, New York, for permission to correspond with their private and house patients in this study.

and asking that they have their mothers personally fill out an enclosed questionnaire. The information requested covered the mother's name and address, general health, age and history of tumors in herself. The specific question was then asked whether or not she nursed the patient. She was definitely informed both in the letter and on the questionnaire that a single, though perhaps unsuccessful attempt to nurse the daughter required an affirmative answer. She was also advised that if there were any doubt in her mind, she should not answer the question at all. Under these circumstances, a personal interview was arranged. Request was made for a maternal family history regarding the incidence of tumors and known cancer among the patient's great grandmother, grandmother, aunts and uncles, as well as her siblings, with ages or ages at death.

Since it has been shown experimentally in mice that a minimal quantity of infected milk can transmit the neoplastic tendency to the female offspring, it was necessary to establish two strict rules for answering the questionnaires. The first was that the patient's mother must give the information in every case. The second was that if the mother stated that she had not nursed the patient, a reason for this must be obtained either by personal interview or by detailed letter. Thus, confirmation that she had not nursed the patient even once was received. Also, other possible sources of human breast milk, such as wet-nursing and breast-milk banks, were eliminated. In a few cases an originally negative reply became affirmative under this close scrutiny. A few other cases of probable negative replies were eliminated from the study for lack of a recalled definite reason why nursing had not been attempted. I am satisfied that in all the cases reported the mother was sure that the daughter in question had never been allowed any human breast milk (Table 1).

TABLE 1. *Data on Breast Feeding.*

PATIENT	AGE OF PATIENT	CHILDREN IN FAMILY	PATIENT'S POSITION IN FAMILY	AGE OF MOTHER	STATEMENT OF MOTHER
	yr.			*yr.*	
Patients with cancer:					
L. M.	29	8	8	70	"I was very ill. L. M. was well started on cow's milk when I was better."
S. K.	46	1	1	75	"Completely inverted nipples. Obstetrician said no use even trying."
L. B.	35	1	1	75	'I had absolutely no milk. First food from selected cow kept for her use. Am sure L. B. never nursed from my breast."
E. G.	48	6	5	82	"Did not nurse last two children — was too weak. E. G. did not ever have opportunity to nurse."
I. T.	43	7	6	79	"Second child only one nursed. My mother and 2 aunts died of tuberculosis. Doctors did not think I ought to nurse my children."
E. M.	48	12	10	84	"Always had sore nipples. Used nipple shield on first four. No milk after that."
H. F.	44	3	2	79	"Tried with first child briefly. No milk. Never tried the others. Too weak to try."
B. G.	33	4	2	69	"No milk. Tried nipple shield on first, never even tried the other three."
E. M.	43	4	2	70	"Inverted nipples. Nearly starved the first baby for 1 month. Never tried the other three."
Patients with plastic operation:					
C. M.	44	3	1	68	"C. M. was one of twins. I only nursed the other."
M. S.	40	3	2	70	"Nursed first baby 1 week. Severely inverted nipples. Never tried the others."
H. T.	38	4	4	72	"Had acute Bright's disease at the time. H. T. weighed less than 2 lb. Never nursed or received breast milk."
E. R.	34	7	2	60	"E. R. was a twin. Never tried either of them. Received formula free from City Hall."
M. P.	55	5	2	78	"Had suffered terribly trying to nurse the first. My doctor would not let me try the others."
A. E.	49	3	3	78	"A. E. was an 11-pound baby. I was very sick. She received bottle milk only."
G. C.	41	4	4	78	"Did not nurse any of them. Was so sick they thought I was going to die. Never tried to nurse ever."

RESULTS

The incidence of absence of breast feeding in the 88 cases of known cancer of the female breast is compared with that in the 86 cases of vaginal plastic surgery. Among the patients with cancer 9 (10.2 per cent) had never received any human milk. Among the patients who had had vaginal plastic operations 7 (8.1 per cent) had never received any human breast milk. The average age of the patients with cancer was 41.375 years, with a range of 23 to 66 years, and that of the patients with vaginal plastic operations 41.395 years, with a range of 26 to 61 years.

Among the maternal family histories of the patients with cancer, exclusive of the patients' neoplasms, a total of 87 tumors, of which 20 were known cancers, were reported. Four of these cancers were in mothers of patients under study; 1 was of the breast, 2 of the intestines, and 1 of the skin. Among the maternal family histories of the patients who had had vaginal plastic operations a total of 35 tumors, of which 14 were known cancers, were reported. Only 1 of these cancers was in the mother of a patient under study: a cancer of the skin.

Conclusion

It appears that a woman may develop cancer of the breast without ever having received any human breast milk. Whether or not the daughters of women with mammary cancer are more likely to develop the same disease if they are nursed has not been investigated and from the study here reported may not be inferred.

I am indebted to Drs. George Van S. Smith, John Rock, Arthur T. Hertig and Shields Warren for their suggestions and criticisms throughout the planning and course of this study.

MEDICAL PROGRESS

THE MILK FACTOR IN THE TRANSMISSION OF MAMMARY CARCINOMA

Jerome Berner*

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"CANCER" is a word that carries with it the respect of fear. The physician, and indeed the layman also, is aware of the remarkable ability of a malignant tumor to extend its claws, in the nature of the crab to which it was likened, throughout the body. Carcinoma is the commonest of all cancers and is characterized by its epithelial genesis. This disease does not restrict its activity to any part of the body but attacks almost all the organs. In the female, however, it has been shown to have a predilection for the breast, developing here almost twice as frequently as in any other location. It occurs in about 4 per cent of all adult women. Before the age of twenty-five it is a rare condition, but from then on its incidence increases throughout the whole life span.[1]

Several factors are of importance in an explanation for the etiology of mammary carcinoma. One theory is that inadequate drainage of the duct system, with stagnation and retention of irritating material, might give rise to this condition. A second theory is based on the effect of irregular or abnormal ovarian stimulation. The hypothesis with which this paper is concerned is the role of the so-called milk factor in the transmission of mammary carcinoma from mothers to suckling offspring.

In studying the occurrence of mammary tumors in a family of mice of high tumor incidence one sees a picture that suggests direct genetic inheritance — that is, most offspring of cancerous mothers tend to develop similar tumors. It has been proved, however, that the breast-tumor factor is transmitted via the milk of the nursing mother and not in association with chromosomes, as would be necessary if the factor exerted a genetic influence.[2]

Much work has gone into the definition and identification of the factor. The credit for the original isolation is due Dr. John J. Bittner working in association with the staff of the Jackson Memorial Laboratory of Bar Harbor, Maine.[3] They undertook their first venture into this milk-factor field in 1930, when they attempted to investigate the existence of an extrachromosomal milk influence in mice. They found that such a factor not only affected the natural incidence of spontaneous mammary tumors in the mice under investigation but also extended its influence for more than one generation. The detection of this extrachromosomal influence was accomplished by a comparison of the incidence of spontaneous mammary tumors among the female mice derived from reciprocal crosses between distinct "high tumor" and "low tumor" strains. (It had previously been observed that certain inbred strains of mice showed a characteristically high or low incidence of mammary tumors.) Since, in such reciprocal crosses, the chromosomal constitution of the first generation (F-1) females is always similar (high x low = high low), it follows that any significant difference in tumor incidence between the two types of crosses is extrachromosomal. And experiments involving 532 F-1 females showed an average incidence of mammary tumors of 70.12 per cent when the cross was made between a female from a high tumor strain and a male from a low tumor strain, as compared to the low average incidence of 3.23 per cent when the reciprocal cross was made. That this extrachromosomal influence is transmitted to following generations was clearly indicated by the persistence of this difference in tumor incidence in over 1100 second-generation (F-2) females. By this fact Bittner and his coworkers[3] definitely disproved the mendelian genetic nature of the biologic agents influencing the etiology of spontaneous mammary tumors. They state, however, that "this should not be taken as denial of the existence of chromosomal influence. There is clear evidence that such influence also is present and effective."

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During the next few years the group at Bar Harbor continued work in this field of investigation, but it was not until 1936 that Bittner[4] successfully isolated and defined the nature of the milk-tumor factor. He accomplished this by a series of experiments involving the observation of the effect on the incidence of mammary tumors in high tumor offspring that were nursed by females of a low tumor stock. Among a group of 40 high tumor offspring that were *not* fostered, he observed an almost even division into mice that had developed breast tumors, the group that came down with primary lung tumors and the animals that died nontumorous. These results are not too significant, but when progeny *were fostered* on females that had breast and lung carcinoma more revealing results were obtained. Ten of the 13 progeny (77 per cent) of fostered females that had breast cancer developed similar growths as compared with 4 of the 24 progeny (17 per cent) from fostered females that had lung tumors. This demonstration that the incidence of mammary-gland tumors in mice may be affected by nursing offers an explanation for the so-called extrachromosomal influence in the development of this type of neoplasm.

The summary of the work done during this original period of investigation was presented by Bittner and Little[5] as follows:

> 1. Breast tumor development is dependent primarily on a "breast cancer-producing influence" which is transmitted through the milk of the high breast cancer stock female to her progeny.
> 2. Females of the high breast tumor stock following fostering by low tumor stock mothers showed a marked decrease in their breast tumor incidence.
> 3. Hybrids which have low tumor stock mothers show a low breast-tumor rate, and hybrids which have high tumor stock mothers show a high tumor rate.

Further investigation of the nature and properties of this factor was undertaken by several other laboratories. At the Surgical Pathology Laboratory of Columbia University College of Physicians and Surgeons[6] special efforts were made to transfer the newborn mice from their own mothers to their foster mothers as soon after birth as possible, so that the young mice would get little to none of their own mothers' milk. These carefully controlled experiments demonstrated the highest incidence (76.1 per cent) of mammary carcinoma induced in a low tumor strain by foster nursing that had yet been reported. In the F-1 offspring of these foster-nursed mice the changes in carcinoma incidence persisted. They were, however, somewhat less notable, which suggests that although the influence of the milk factor is transmitted to some degree through successive generations it must be renewed through ingestion of milk itself for each generation of mice if it is to exert its full effect. Dr. Haagensen, who directed the work at Columbia University, also attempted to exclude the possibility of the transfer from mother to offspring of some agent other than milk that might play a part in the development of carcinoma. That the milk itself carried the active carcinogenic principle was demonstrated in his experiments by the development of mammary carcinoma in 42.6 per cent of the mice of low tumor strain fed milk artificially obtained from mothers of high tumor strain. This significant response to no more than 1.0 cc. of the artificially obtained milk indeed provokes speculation upon the nature of an agent that causes the development of a malignant neoplasm in old age though it is introduced into an animal in minute amounts during the first two days of life.

The additional work on the effect of foster nursing on the incidence of mammary carcinoma was conducted at the Royal Victoria Infirmary in England by Miller and Pybus.[7] These investigators demonstrated that the frequency of tumors in low tumor mice fostered by high tumor mothers before twenty-four hours (58.3 per cent) was much greater than that in animals fostered after twenty-four hours (16.7 per cent) and also showed that if the low tumor mice had spent from six to twelve days with their own mothers before being fostered, they were no longer susceptible to the action of the milk influence, although they were able to transmit it to their young. These observations indicate the close relation of the development and transmission of mammary tumors to the time of fostering, and especially illustrate the urgency of immediate removal of offspring from parents in order to effect any significant modification of the tumor incidence.

Now that many workers had demonstrated what the mammary tumor agent could do, the task of describing its physical, chemical and biologic properties yet remained. Andervont and Bryan[8] showed that the agent could be obtained from filtered extracts of mammary tumors and likened it to a virus in this respect. Other viral properties ascribed to the milk factor include its ability to produce neutralizing antibodies, its survival in cold and its lack of resistance to heat. This inactivation of the tumor agent by exposure to a temperature of 61°C. for thirty minutes is quite significant in that it clearly indicates how the agent might be destroyed: by ordinary pasteurization. Additional properties of the agent were described by Barnum and his co-workers,[9] who showed that the agent is stable at pH values between 5.0 and 10.2, that it is not inactivated by petroleum ether or acetone and not soluble in these solvents, and that it is partially precipitated by salmine, a basic protein, at pH of 5.5 and 6.8. Thorough investigation[8] of the biologic nature of the tumor agent revealed that it was one hundred and sixty times as infective by intraperitoneal administration as by oral ingestion, that the agent could be demonstrated in inbred strains, that it could produce tumors in mice of unknown ancestry and that it could be neutralized by specific antiserums. The last property was demonstrated

as follows: after injection of the agent — that is, a mouse-mammary-carcinoma extract — into a rabbit, no tumors, of course, develop in the animals; the serum of such a rabbit, however, acquires the property of neutralizing the agent in vitro. When such an immune serum is incubated in a test tube at room temperature for two hours with mouse-mammary-carcinoma agent, it neutralizes it; the mixture injected into mice will not produce tumors. The neutralization is specific; normal rabbit serum, for instance, will not neutralize the tumor agent[8, 10]; nor will the mammary-carcinoma agent be neutralized by a serum obtained from a rabbit that had been injected with a different tumor[8] or with normal mouse organs.[10]

That no aspect in the complex nature of this agent remain uninvestigated, Bittner and his associates,[11, 12] in a series of experiments beginning in 1945, undertook the study of the survival of the milk agent via transplanted tumor tissue. They showed that the agent persisted in association with tumor transplants carried through as many as ten serial passages in mice that did not themselves carry the milk influence but had the inherited susceptibility for spontaneous mammary cancer. This experiment indicated that the agent must have been continually produced within the transplant tumor cells. Not only was the transplantability of mammary tumors not dependent upon the presence of the milk agent but also, as demonstrated by Bittner,[13] the tumors grew as well in mice possessing an agent from a different source — that is, a different strain — as in animals with the agent from the same source present in the tumor.

A consequence of the detailed description of the physical, chemical and biologic properties of the milk factor was the even more exacting task of actually separating and isolating this most potent agent, whose actions had been demonstrated but whose features were still obscured in the depths of matter. In the attempt to isolate the agent hardly a stone was left unturned — that is, by means of tissue sources. The agent was ultimately sedimented from extracts of mammary glands[14] and from mouse milk[15] and also demonstrated in whole blood, spleen and thymus,[16] as well as in liver.[17] Barnum et al.[18] showed that lactating mammary glands were a most potent source of the breast-tumor milk agent. Extracts of this tissue gave rise to tumors even at dilutions of a millionfold. These experiments were quite revealing, but it was not until Passey,[19] in England, undertook electron-microscope studies of milk from high-breast-cancer-strain mice that some insight into the actual morphologic picture of the milk agent was attained. He described particles, 200 to 350 Å in diameter, that were separated by ultracentrifugation from milk of high-breast-cancer-strain mice. Porter and Thompson,[20] however, working at the Rockefeller Institute, criticized Passey's work on the grounds that his procedures of preparing water extracts of desiccated tissue might very possibly alter the agent to the extent that it might easily be confused in microscopy with particulate elements present in the cytoplasm of all cells. These investigators studied the cells themselves and reported the finding of "an unusual particulate body in association with the cells." They described these particles as follows:

> A spherical shape and a double structure consisting of a dense center and a less dense outer zone. The diameter of the central dense portion is fairly uniform from particle to particle, averaging approximately 75 millimicrons; whereas the outside, whole particle diameter is more variable and averages about 130 millimicrons.

The exact significance of these particles is still speculation, but these workers interpret their findings as follows:

> So far, the particles have been found only in association with the epithelial cells of the cultures. They are apparently not derived from the culture media. All in all the findings are consonant with the view that the particles represent the milk agent.

The most recent and by far most extensive study into the isolation of the virus of mouse mammary carcinoma is now being conducted by Graff and his co-workers[21] at the College of Physicians and Surgeons and Presbyterian Hospital in New York and also at the Rockefeller Institute. These investigators observed that the milk agent is ordinarily transmitted by ingestion and advanced the hypothesis that the agent might be resistant to the action of the digestive enzymes normally present in the stomach and intestines. They applied this theory by using crystalline chymotrypsin for the hydrolysis of the proteins accompanying the agent in the milk. Thus, having successfully freed the agent from the hold of the interfering casein particles, they were more readily able to isolate it by differential sedimentation. The employment of this technic resulted in the isolation from the milk of high-cancer-strain mice of a substance consisting of particles that had the dimensions and properties of a virus. When inoculated into mice from a strain in which mammary carcinoma was rare, this material induced the disease. It was also demonstrated that similar particles could be recovered from the milk of these low-cancer-strain mice in which the disease had been induced by foster nursing. The milk of the nonfostered control mice of this low tumor strain, however, revealed no such characteristic particles. Work is currently being done to determine whether or not infectivity is associated *exclusively* with these sedimenting particles.

The studies of Hellwig[22] upon tissue extracts from human tumors raised the question of whether the extracted particles were indeed virus-like causative agents of extraneous origin, as postulated by previous investigators. His studies revealed globular bodies in most extracts of tumors, as well as a definite difference in size between cancerous and

benign specimens. The particles in the benign tumor extracts seldom exceeded 60 millimicrons whereas those from cancerous tissue often exceeded 80 millimicrons. Since Hellwig had previously been able to demonstrate similar spherical bodies in cerebrospinal fluid from persons without tumors, he believed that the particles with a diameter of less than 60 millimicrons were apparently normal cell constituents and represented globular proteins rather than viruses. He suggested that the larger particles found in malignant tumors were probably aggregates of the cytoplasmic globules due to an alteration in the colloidal state of the cancer cell.

Bonser[23] has extended the use of the microscope in studying the various aspects of the problem of the milk factor from that of investigating the morphologic nature of the agent itself to a study of the micropathology of the cancerous lesion. She reveals

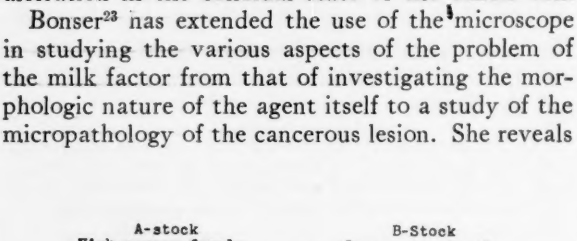

FIGURE 1. *Influences Necessary for Development of Breast Cancer in Mice of High Tumor Strain.*

A breast tumor should theoretically result when all influences are active (shaded area), but when one or more of the influences are inactive (unshaded), the mouse should be noncancerous.

that in the mouse intra-acinous carcinoma was the first and most frequent form of cancer to be observed and was accompanied in a small number of cases by an intraduct form of the neoplasm. The milk factor was shown to have its effect primarily upon the acini, leading to a high degree of acinous proliferation and intra-acinous and extra-acinous carcinoma.

The vast amount of work that had been done in describing the nature and properties of this cancer-producing influence still left unsolved the mode of action of the agent. What was its exact role as a factor in the formation of a carcinoma of the breast? Did it alone provoke the development of cancer, or was it one of several factors that exerted a combined influence? Bittner[24] adopted the latter point of view and propounded the theory that three influences were necessary for the development of breast cancer in high-tumor-strain mice: a breast-cancer-producing influence that is normally obtained in the milk during nursing of a potentially cancerous female; a breast-cancer susceptibility transmitted by males and females of high tumor strain to progeny and inherited as a single dominant factor; and the growth of the mammary glands to the point where cancerous change may take place as the result of stimulation of ovarian hormones.

The equipotentiality of these factors was demonstrated by Bittner diagrammatically (Fig. 1). Bittner qualified this statement by explaining that a low tumor strain, though lacking the susceptibility to development of breast cancer, readily passes on to other mice any milk influence that it might have received through foster nursing.

This original theory[25] of cancer development, which assigned roles of equal influence to the milk factor, inherited susceptibility and hormonal stimulation, was variously interpreted by the many workers who investigated Bittner's findings. Andervont[26] substantiated Bittner's point of view, but went farther in suggesting that some tumors might develop in the absence of or with subthreshold amounts of the milk influence. In these cases he proposed that a deficiency of the milk influence might have been overcome by an increase in hormonal stimulation and inherited susceptibility. This introduces the idea of a quantitative balance existing among the three influences.

Heston and his co-workers[27] emphasized the importance of the genetic influence. They explained the failure of some strains of mice to develop mammary tumors but to be able to propagate and transmit the milk agent upon the basis of assumption that two sets of genetic factors are involved. Bittner[24] had previously stated that a single dominant genetic factor was involved and that it was concerned with susceptibility. These workers claimed, however, that one factor determined whether or not the agent will be propagated and that the second factor influenced the susceptibility of the mammary-tissue cell to the carcinogenic action of the agent. They maintained that both factors would have to be present for a tumor to appear. The fundamental theory of breast-cancer development as outlined by these investigators stated that the tumor development is governed largely by a cytoplasmic factor, the milk agent, which in turn is under the control of the nucleus with its chromosomal factors. They did not minimize the importance of the milk agent per se, but rather stressed the importance of the genetic factors and of their intimate relation to the milk agent. The experimental basis for their concept lies in the demonstration of the ability to vary the tumor incidence from above 90 per cent to approximately 50 per cent in females with uniform extrachromosomal factors by alteration of the genetic factors alone. The effect of the genetic influence is also manifested by the late appearance of mammary tumors in certain breeds of mice and the persistence of this late age of development in the first-generation offspring.[6] This introduces the idea of constitutional factors associated with particular mice strains. A further emphasis of the genetic influence was made by Bittner[13] himself, who demonstrated in one experiment that the growth of mammary cancer in mice, as determined by its transplantability,

was dependent upon the genetic relation of the host and the tumor cell and not upon the mammary-tumor milk agent.

That the inherited susceptibility is more important than the concentration of the milk agent in determining the development of mammary carcinoma in mice was again experimentally shown by Warner and associates[28] in a series of reciprocal matings. This influence of inherited susceptibility may be modified by the age at infection. It has been observed that when mice of a genetically high tumor strain but lacking in the milk agent are infected with the tumor virus after they are a few months of age they develop a much lower incidence of mammary carcinoma than if infection occurs when they are under a month of age. It seems, then, that as they grow older, genetically susceptible mice that lack the milk agent become less "susceptible" to the milk-agent virus, at least as far as the subsequent development of mammary tumors is concerned. This relative nonsusceptibility of older mice is not due to greater mammary-gland development at the time of virus infection but probably reflects a more general increased resistance of older mice to the influence of "carcinogens."[29]

In contrast to these several findings, which emphasized the influence of the genetic factors, Murray and Little[30] concluded their investigations with the following statement: "Some extrachromosomal influence, which is ten times as powerful as any possible chromosomal factor, is instrumental in determining whether or not mammary carcinoma appears in the first out-cross generations."

In view of these many varied experimental observations and associated interpretations of the relative influence of factors producing mammary tumors, it is no wonder that some confusion arose. Heston[31] summarized the situation as follows: "Whereas in the past there was an inclination to place the milk agent, the hormones, and the genetic constitution more or less parallel, from more recent findings it now appears that we should picture the genes in a more basic position, with their actions becoming manifest through at least three gene-action paths, the first involving the milk agent, the second the hormonal stimulation, and the third the susceptibility of the mammary tissue."

That mammary carcinoma occupies a unique position in the origin of diseases was refuted by Gross.[32] He stated that hormonal stimulation and the susceptibility of the host, which is essentially inherited, seem, at least in principle, no more important in the origin of mammary carcinoma than they are in the acquisition of diseases caused by various micro-organisms and viruses.

For the past nineteen years much time and effort has gone into the isolation and demonstration of the mode of action of the virus-like mammary-tumor agent. Many investigators next undertook the task of interpreting and applying the vast collection of facts that had been accumulated through years of extensive research. These workers were now confronted with many perplexing problems. One of the most striking is that of interpreting the very long interval between the exposure of the host to the transmissible agent (early infancy) and the actual appearance of symptoms of the disease — that is, the formation of the tumor. It appears possible to assume that the invisible tumor agent is transmitted from one animal to another in some inactive form, and that it remains inactive and harmless during most of the life span of the host. Usually, at the end of the host's life cycle, conditions may develop that, at least in some cases, may prompt an activation of the hitherto inactive tumor agent. The conditions favoring such activation have not yet been fully determined, and are poorly understood. Old age and certain hormonal stimulations are some of these conditions that are known.

When the etiology of mammary carcinoma in mice had been definitely established, the problem arose of determining whether there was a practical method of prophylaxis for this condition. Gross[2] stated that the development of mammary carcinomas in otherwise susceptible mice of the tumor families can be prevented by the simple measure of isolating the newly born animals from their tumor-agent-carrying mothers and transferring them for the purpose of nursing to females whose milk is free from the invisible mammary-carcinoma agent. They live their normal life spans and do not develop breast tumors. Moreover, their milk is also free from the tumor agent; they can, in due time, nurse their own litters naturally, without transmitting to them the seed of the fatal disease.

A new outlook upon the manner of transmission of mammary carcinoma was afforded by a series of studies into the immunologic properties of the tumor agent. By this approach Gross[33] was able to reveal that three apparently independent mammary carcinomas developing spontaneously in female descendants of a high tumor line of mice were actually immunologically identical. This observation, coupled with the knowledge of the mode of transmission of a tumor-producing factor via the milk of the nursing females, leads to the conceivable conclusion that mammary carcinoma of mice is not a "spontaneous" condition, but that each tumor can be traced to another, similar neoplasm. In the light of this concept that the tumors are not "spontaneous" in origin, but rather represent successive links in a host-to-host transmission of the same neoplasm, one sees the beginning of Gross's[2] theory of a "vertical epidemic" of mammary carcinoma. This theory may best be demonstrated by a comparison of the pattern of transmission of mammary carcinoma of mice with that of many common communicable diseases. The several differences between the two patterns is readily apparent. In measles, smallpox or typhoid fever the transmission of the

infectious agent occurs among hosts that, in most cases at least, belong to the same generation — "horizontal epidemic"; thus, an infected host placed in close quarters with other healthy but susceptible persons of practically any age often transmits the infecting agent to its companions. In mouse mammary carcinoma, however, the causative agent, as a rule, is transmitted among hosts belonging to successive generations. A mouse carrying the tumor agent and bearing a large, exposed, perhaps already ulcerated mammary carcinoma, can be placed in the same cage with healthy, susceptible mice, and yet no transmission of the disease will result. The same tumor-bearing mouse, however, will transmit the tumor agent, through milk, to her own daughters, and through these to her granddaughters, great-granddaughters and so forth — that is, to hosts of successive generations. The term "vertical epidemic" has been suggested for this type of transmission of extraneous parasitic agents. The pattern of "vertical" transmission of pathogenic agents is not limited to the virus of mammary carcinoma of the mouse, but is also followed by many other parasites, particularly in plants and in insects.

Despite the difference in the mode of transmission in "vertical" and "horizontal" epidemics, these two patterns are similar in that in both an animal may harbor the agent, and actually transmit it to other hosts, and never show any symptoms of the disease. The carrier state in mouse mammary carcinoma is seen as a "skipping" of an entire generation, since the transmission occurs between hosts of successive generations. This apparent absence of the disease in one generation with its reappearance in subsequent generations may be explained by the death of the animal transmitting the agent before it manifests any sign of the tumor. It would already, however, have passed on the agent to its offspring. Recent observations also suggest that mice actually carrying the agent may live their full life span without developing breast tumors, provided their caloric food intake is restricted.[34-36]

This new approach to the problem of cancer via the "vertical-epidemic" theory carries with it many implications. It now appears difficult to consider that the mouse mammary carcinoma develops "spontaneously." Breast cancer in mice appears to be no more "spontaneous" than a case of tuberculosis or typhoid fever. It is not known at present whether there is any communicable disease that would develop *de novo*. There is no convincing evidence to support the idea of spontaneous generation of any parasitic agents, no matter how small they may be. In many cases, especially in human beings, cancer *appears* to be a spontaneous disease. This false impression may result from the limitation of available information to about three generations of women. One usually remains ignorant of the portion of the story before the grandmothers and after the daughters in any one family. But in mouse mammary carcinoma a more extensive picture of the family history can be studied, and it reveals that the gaps in the otherwise continuous appearance of the cancer are merely due to the submergence of the virus to a carrier state. If adequate records were available, every case of mammary carcinoma in mice could be traced to a previous occurrence of the disease.[2]

But can all this information be applied to the problem of breast cancer in the human being? This was the foremost question that was asked of the investigators in this field. Heston[31] seems to believe that the greatest contribution to the problem of breast cancer in human beings that has been made by the laboratory investigations has been the conditioning of the view of the probable nature of the human cancer problem. He adds, however, that one must consider that at present a milk agent has *not* been demonstrated for breast cancer in man and that furthermore there is little reason to suspect that, if an extrachromosomal agent is demonstrated, it would be any more likely to be transmitted through the milk than through any one of a number of other possible channels, including the uterine wall or the cytoplasm of the egg. Another observation raising a question of doubt about the similarity of the human and mouse situations was that expressed by Bonser,[23] who demonstrated that the histologic nature of the human type of mammary tumor was different from that found in mice. This criterion of the nature of tumors was contested by Gross,[33] who showed through a series of experiments that the immunologic identity of a tumor may be a more reliable and constant characteristic than its morphologic appearance. He also stated that at present no exact answer is possible to the question of whether the factor responsible for breast cancer that is transmitted via the milk of nursing mothers is limited to mice or is valid also for other species of mammals including man. The evidence presented by Horne elsewhere in this issue of the *Journal*, however, seems to indicate that susceptibility to human mammary cancer is not so transmitted. Until more information on experimental cancer is obtained, only a tentative assumption based on theoretical considerations can be ventured. It is possible to assume, however, that mammary carcinoma of mice does not represent a form of cancer different from breast cancer in other mammals.[2] That no tumor agent has been identified in the human being is no wonder, considering the great number of possible complicating genetic influences. It is reasonable to expect, however, that the breast-tumor problem in the human species, like that in the mouse, may be one in cell physiology involving an interrelation between genetic action and a cytoplasmic determiner similar to the milk agent. This concept offers a hope that such factors can be identified.[27]

Assuming that the picture of human breast cancer is similar to that described, which is not too remote a possibility, one could readily suggest a feasible plan for preventing human breast cancer by the simple method of artificial feeding of infants born to mothers having a family history of tumors.

There is at present no way of determining the presence of the tumor agent in the milk of a nursing female mouse except by checking her family record for the occurrence of tumors. A female mouse whose milk contains the tumor agent is in perfect health at the time of nursing; she will develop mammary carcinoma upon reaching middle age, if she develops a tumor at all; she may die before she reaches the tumor age; on the other hand, she may live her normal life span and yet never develop a tumor (although she carries and transmits the tumor agent) if her diet is restricted[34-36] so as to cut her caloric intake by 30 to 50 per cent. The only way to determine whether she carries and transmits the tumor agent is to check her family record. Her mother might have died without a tumor, as well as her grandmother, but perhaps a sister of her mother, or her great-grandmother, developed a mammary carcinoma.

If a parallel with human cancer may still be drawn, a history of breast cancer in the family of a nursing and apparently healthy mother may indicate the presence of a tumor agent in her milk. Since no more than a few hours of breast feeding may effect a transfer of the tumor factor, the conclusion would be justified that breast feeding in such cases should be abandoned *from birth*. It might suffice to omit breast nursing for a single generation to interrupt the flow of the virus. Breast feeding could than be resumed in succeeding generations.

This proposed method of preventing breast cancer has not met with universal approval. One of the most emphatic opponents to the plan is Macklin,[37] who presents the following arguments:

> There is as yet no proof that a baby *exclusively* fed with artificial formulas from the moment of birth on has as good a chance of survival as a baby that is breast fed — at least one breast fed in the early months of infancy.
>
> Experimental evidence shows that stagnation of milk in the breast plays a role in producing breast cancer in mice. By this token one would be subjecting the mothers of this generation to an increased risk of breast cancer to prevent the child of the next generation from having the same condition.
>
> The late onset of breast cancer in women (after the age of forty-five) and the apparent gaps in the transmission make it most difficult to urge granddaughters to refrain from nursing their children because their grandmother had breast cancer. And if the grandmother died before the cancer developed, how could the granddaughters be warned against nursing their offspring?

These objections, in addition to the one that eradication of breast cancer may be replaced by an increased frequency of cancer in other organs, can be very adequately answered. In the first place, infants fed with prepared cow's milk or with commercially available substitutes for human milk can be raised with no increase in mortality. Pasteurized or briefly boiled *human* milk could be safely used for this purpose, since in mice, at least, the tumor virus does not resist pasteurization.[8, 9] For the second argument there is no experimental support.[38] Besides, breast cancer will *not* develop in animals free from the transmissible tumor agent, regardless of stagnation. Bittner[39] reported that experimentally produced stagnation *in a cancerous strain of mice* actually decreased the incidence and delayed the time of appearance of the breast cancer. The reply to the third objection lies in a very accurate and complete family history, especially one of tumors. And the last challenge to the plan does not appear to have any reliable experimental or clinical support. One is tempted to compare such a statement with an assumption that the eradication of pulmonary tuberculosis would precipitate tuberculosis of the intestines or of bones.

Gross[38] comments on the possibility of preventing breast cancer in women as follows:

> Breast cancer in mice is transmitted through milk from mothers to daughters and can be for all practical purposes exterminated by the simple measure of foster nursing of one single generation. Difficult and time consuming studies are necessary to find out whether human breast cancer is also transmitted through the milk of nursing mothers. It will take some 50 or 100 years to carry out such a research project. If breast cancer in women is caused by factors similar to mammary carcinoma in mice, some fifteen to twenty-five thousand women could thus be saved from death each year in this country alone.[40]

A much more pessimistic outlook is held by Macklin,[37] whose doubts are quite strongly expressed: "We cannot breed out cancer, whether it be conditioned by a gene or a virus, unless it be a form of cancer that arises in early childhood before the age of procreation, or unless we stop all the race from breeding or all women from nursing."

All the observations concerning the mammary-tumor agent made above are as yet insufficient for any generalized conclusions to be drawn. It is possible, nevertheless, to advance a working hypothesis[32] about the origin of at least certain malignant neoplasms in animals and also in man.

There may be a group of transmissible agents causing tumors in animals and in man; these agents would be so small as to be invisible under an ordinary, optical microscope; and they would possess many of the characteristics of pathogenic viruses. The agents would be fundamentally similar in certain features of their behavior. Thus, they

would attack certain groups of cells within certain hosts and would live and multiply in such cells; as a rule, these tumor agents would be frugal and moderate in their requirements, and would not apparently injure the host. For obscure reasons, however, the pathogenicity of the agent may sometimes change during the latter part of the life of the host, and a tumor would then develop, usually sealing the fate of the host — that is, growing progressively, and, if not treated, killing the host. The survival of the agent would in the meantime have been secured, however, by transmission to another host occurring as a rule prior to the appearance of symptoms of a tumor in the transmitting person.

One of the most striking features of the pattern of natural transmission of these agents would be their faculty to pass "vertically," from one host to another of successive generations. The generation-to-generation transmission, with occasional "skipping" of intermediate carriers, — that is, with skipping of generations, — would make the task of tracing the epidemiologic course of the tumor agent extremely difficult. Although the tumors would in principle belong to the general group of "communicable" disease, transmission would occur as a rule among hosts of successive generations.

The agent would appear to be able to attack new hosts efficiently either in their embryonic stage or in their infancy. A long, asymptomatic phase of the disease would then follow, during which the host would transmit the agent to the succeeding generation. The activation of the hitherto latent agent in the transmitting host would then follow, though it would not always have to occur. The activation of the tumor agent could be prompted by a number of general or local, nonspecific, factors such as those related to aging, by hormonal stimuli or metabolic disturbances or by exposure to irradiation or to certain systemic poisons. (This hypothesis indicates Gross's answer to the oft asked questions[41] of why tumors develop in animals subjected to prolonged irradiation with roentgen rays or with radium and by application of many carcinogenic chemicals.) In some cases, on the other hand, the activation of the agent could be prevented by hormonal influences, by a restricted food intake or perhaps by some other as yet obscure factors.

Since tumors can be produced almost at will, at least in mice, by the application of many carcinogenic agents, the question is raised[41] whether it is possible that all these animals are carriers of an inactive tumor virus that is being activated by the carcinogenic agent. Gross[2] stresses the fact that, in the mouse at least, hormonal stimuli will prompt the development of breast cancer in male mice otherwise free from cancer only if the mammary-carcinoma virus is present in the host. If this is true for other carcinogenic factors, the assumption is necessary that the tumor virus or viruses are so widely spread in the animal kingdom that most animals carry one or another of them in their cells without, in most cases, showing any tumors.

Now that the laboratory work regarding the definition of the tumor agent has been carried just about to completion, except for the electron-microscope studies that are currently being conducted, one can only speculate about the effect that the sum total of all this research will have upon knowledge of the incidence of human breast cancer. Only by informing the women of the nation of the implications of the facts discovered and emphasizing the importance of following the recommendations of Gross — women with family histories of breast tumors are not to nurse their children — can one take steps toward the application of the theory that mammary carcinoma is actually transmitted via the milk of the nursing mother. Conclusive proof that the human situation is indeed analogous to that in mice will only be obtained after many years of thorough investigation into family histories of breast tumors and accurate tracings of the occurrence of similar tumors in the offspring of these and of nontumorous families. Though definite proof of this theory is lacking, the mother's sacrifice of refraining from nursing her children would be slight if she could thereby ensure future generations against the scourge of breast cancer.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 36361

PRESENTATION OF CASE

First admission. A fifteen-year-old boy was admitted to the hospital because of fever, cough and pleurisy.

The patient had been in excellent health until one month before admission, when he suffered the insidious onset of mild fever, lack of energy, mild headache and general malaise. After a week the symptoms became somewhat worse, with daily temperature spikes to 101°F. and a nonproductive cough. At this time the white-cell count was 8800, with 70 per cent neutrophils, cold agglutinins were negative, and a chest x-ray film revealed an area of hazy density at the right base near the midline extending from the hilus to the diaphragm. Penicillin was started, but there was no clinical improvement. A second chest x-ray film a week later showed beginning clearing near the base but some spread from the hilus. After eight days the penicillin was discontinued, and aureomycin therapy instituted. A slow defervescence occurred over two days, and he remained afebrile for four days. There was some diminution of cough but the white-cell count was 12,800, with 75 per cent neutrophils and 8 per cent eosinophils. After a week of aureomycin therapy dullness to percussion was noted at the right-lung base, and rales became audible in this region. The fever increased, and daily temperature spikes to 103°F. occurred. One or two chills were noted. A chest x-ray film showed both clearing and extension of the process in the right lung, with questionable cavity formation. Two days later episodes of pleuritic pain over the right lower chest occurred. The white-cell count was 13,800, with 72 per cent neutrophils, and cold agglutinins were again negative. A single sputum examination for acid-fast bacilli was negative.

The family history was noncontributory. A week prior to the present illness the patient had helped to skin a rabbit shot by a friend.

Physical examination revealed a chronically ill boy with splinting of the right thorax. There was dullness at the right-lung base posteriorly, with a friction rub, moist rales and increased pectoriloquy. The remainder of the examination was negative.

The temperature was 98.6°F., the pulse 80, and the respirations 22. The blood pressure was 104 systolic, 50 diastolic.

Urinalyses were negative. The hemoglobin varied from 11.4 to 12.6 gm., and the white-cell counts ranged from 10,500 to 9300, with 60 to 72 per cent neutrophils. The blood sedimentation rate was 10 mm. in one hour. A throat culture contained abundant alpha-hemolytic streptococci. Culture of bronchial secretions contained colon bacilli. A blood culture was sterile. Agglutination tests for tularemia were negative in a 1:10 dilution. Repeated chest films (Fig. 1) showed progressive clearing of density in the right lower lobe and the presence of three distinct thin-walled cavities con-

taining fluid. There was some suggestion of narrowing of the right-main-stem bronchus. Bronchoscopy was negative.

There was progressive clinical improvement, and on discharge ten days later the patient was symptom free despite x-ray evidence of diminished size of the right lower lobe and the continued presence of cavities.

Second admission (one year later). In the interval he had continued to improve. Chest x-ray films in the interval were normal, showing no evidence of cavitation. Three weeks before entry he contracted an upper respiratory infection, with malaise and mild fever, and he was given penicillin and aureomycin, with marked clinical improvement. Two days before admission he developed a hacking cough, with leukocytosis, chills, fever and signs of pleurisy at the right-lung base. A chest film showed recurrence of the cavities within the right lower lobe, and he was promptly readmitted to the hospital.

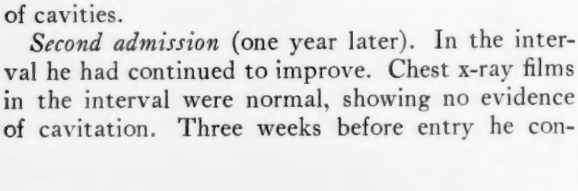

FIGURE 1.

Physical examination again demonstrated a chronically ill boy with signs of dullness, diminished fremitus, amphoric breath sounds, pectoriloquy and friction rub over the right lower thorax posteriorly. The white-cell count was 15,000, with 85 per cent neutrophils. Cultures of the urine and sputum were negative. An x-ray film of the chest showed extensive collapse and consolidation of the right lower lobe, with an apparent abscess cavity at the apex of the lobe.

The temperature was 101°F., the pulse 95, and the respirations 25. The blood pressure was 100 systolic, 60 diastolic.

There was prompt clinical improvement, and he was discharged on the fifth day to return for surgery.

Third admission (one month later). In the interval he had felt well and had been free of cough and fever. There was slight dullness, diminished breath sounds and fine moist rales over the right lower lung posteriorly.

Examination of the blood showed a hemoglobin of 14.8 gm., and a white-cell count of 5000, with 48 per cent neutrophils. Chest x-ray films showed considerable collapse of the area in the right lower lobe that had previously been consolidated. The area could now be localized to the posterior basal segment and contained multiple cystic cavities.

An operation was performed on the fifth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. ARTHUR S. PIER*: I find this a very difficult case, and after reading the history I wonder if I really have the foggiest idea of what was wrong with this boy. Before looking at the x-ray films I would like to try to piece certain bits of evidence together. What was the first illness that struck the patient pretty much out of the blue after five years of good health? At first glance it looks like a primary atypical pneumonia, with the insidious onset, over a period of a few days, of mild fever, malaise, headache, a nonproductive cough and a normal white-cell count. The x-ray films first showed hazy density spreading out from the hilus and then showed a progressive clearing in one area and extension of the process to another. That is all quite characteristic of a primary atypical pneumonia, but as I read on that diagnosis seemed to be less tenable. The fever was too spiking. Cold-agglutination tests were negative twice. Cold agglutinins become positive usually in the second week of that disease; although the first test may have been taken too soon, the second was certainly taken at a time when it might be expected to be positive. Cold agglutinins are positive in perhaps 50 to 60 per cent of the cases of primary atypical pneumonia and tend to be positive in more severe cases. The response to aureomycin, which I gather he received in generous amounts over a long period, was not at all dramatic — nowhere near as good as one would expect to see in a case of primary atypical pneumonia. On the whole I think that perhaps the disease began as an atypical pneumonia and a bacterial infection became superimposed.

Assuming that the patient did have a bacterial bronchopneumonia, why did it go on for so long? Actually, although he was receiving both penicillin and aureomycin, it was about forty days before he became afebrile and symptom free, and also he developed cavities during that time. All this is rather suggestive to me of some bronchial obstruction that was not allowing adequate drainage. It

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is interesting in this regard that on admission to the hospital he was described as having increased pectoriloquy. Pectoriloquy is an interesting sign, but it rather puzzles me here. It would mean of course that the bronchus was not closed entirely, since no voice sounds, whispered sounds or breath sounds could be heard in that case.

There is another form of pneumonia that apparently was considered here and that is tularemia pneumonia. Tularemia is a disease with a rapid incubation period, — a matter of several days, — and the patient handled a dead rabbit a week before he became sick. In the tularemia cases that I have read about, pneumonia is described as occurring in 10 to 25 per cent. It is a pneumonia that is often indistinguishable in its early course and x-ray picture from a primary atypical pneumonia, often produces hacking, nonproductive cough and shows a white-cell count that is normal or only slightly elevated, with an essentially normal differential. It can be relatively mild or very severe and fulminating and end fatally. It may last twenty, thirty or forty days, producing pleuritis, forming cavities and abscesses and ending up with a good deal of pulmonary fibrosis in the affected lobe with all the sequelae that arise therefrom. I think a tularemia pneumonia is very attractive here, but I shall have to rule it out because of the negative tularemia agglutinins. In the cases that I have reviewed, the agglutination tests were invariably positive after the third week of the disease. Two patients who died within a three-week period had negative agglutinins. The patient under discussion had no skin lesions and no lymphadenopathy suggestive of tularemia, although tularemia pneumonia is said to occur more frequently in the so-called typhoid tularemia that has no skin lesions and no lymphadenopathy.

Could the patient possibly have had just a primary bronchiectasis giving rise to a pneumonitis? That thought is not very likely because he had been well for fifteen years with no cough, no sputum and no clubbing of the fingers.

One of the uncommon conditions, such as a fungous infection of the lung, I think, is unlikely. It all started rather fast and subsided rather fast for anything like actinomycosis.

Tuberculosis was pretty well ruled out by the negative sputum examination and by the fact that he became quite well after forty days and had no cough during the next year. If he had had a tuberculous bronchitis, he would have had a bad cough and not done well at all in the interim.

About all I am able to say about this first illness is that there was a pneumonitis, possibly starting as a virus pneumonitis, with bacterial infection superimposed, and that it lasted as long as it did very likely because of inadequate bronchial drainage due to partial bronchial obstruction that enabled lung tissue to break down to form cavities or a cystic bronchiectasis. I gather that the physicians who saw the patient reasoned the same way because a bronchoscopy was carried out at some time during the first admission. I am surprised that the bronchoscopy was negative.

I am also fascinated by the fact that the bronchial secretions contained colon bacilli, which I think is an extraordinary organism to find in pneumonia. Dr. Lewis Kane has told me that a pneumonia due to colon bacilli is probably always an aspiration affair. It takes a good many organisms to cause a pneumonia, and there probably must be underlying disease in the lung. Of course, we see colon bacilli growing out in many queer places in people who have received huge doses of penicillin, but I do not believe this boy was receiving huge doses of penicillin at that time.

I think it is very interesting that after the severe onset the cavity apparently disappeared for a year, for the x-ray films were said to be normal. May we look at the x-ray films now?

Dr. Stanley M. Wyman: I am sorry we do not have the films that are described as clear. Perhaps they were taken somewhere else. In the films taken during the first admission the process is confined to the distribution of the lower lobe and can be seen in both projections lying very far posteriorly against the chest wall. At the time this film was taken three very distinct, quite thin-walled cavities were seen in the lower lobe. There is no appreciable fluid in the pleural cavity on either side. The other lung fields appear clear.

Four days later there has been some emptying of the cavities, which again appear very thin walled. One year later at the time of the second admission, there is a very large homogeneous area of density in the distribution of the lower lobe, with now only one fluid level seen very high up at the site of the uppermost cavity. The last films show increased linear and mottled density in the right lower lobe involving the posterior basal segment, and there is a large, unusual rarefaction above this, apparently in the superior segment of the lower lobe. It looks like a huge bullous area — a huge bleb.

Dr. Pier: Do you see any evidence of this suggestion of main-bronchus constriction that is described in the beginning?

Dr. Wyman: The right main bronchus can be seen on several films, and it looks to me to be within normal limits. I cannot, however, exclude some disease down in the lower-lobe branches beyond the point where the middle lobe has been given off. There might be something down there that I cannot see.

Dr. Pier: After the first examination here I gather that the patient went home and was relatively symptom free. Although he was symptom free, one wonders whether he was as well as he ap-

peared to be. A year later he had what seemed to be a relatively harmless upper respiratory infection that turned into a pneumonitis in the right lower lobe — the same place that he had it before. That again makes one suspect that the right lower lobe was susceptible to disease, possibly because the first illness caused some scarring — fibrous bronchiectasis — that allowed infection to settle there a year later. However, I think it is better to assume that he had some trouble there to begin with that was responsible for both these episodes of pneumonia.

The basic trouble was probably a bronchial obstruction. What sort of obstruction was he likely to have? There was no history of aspiration of a foreign body. It seems to me that the best bet is adenoma. I think it is very rash to make a diagnosis of a bronchial adenoma in the face of a negative bronchoscopy. Bronchial adenomas almost invariably occur in the major bronchi and are easily visible to the bronchoscopist. I think in the series of adenomas at this hospital there have been perhaps only 2 that have not been seen on bronchoscopy — 2 that have been in smaller bronchi so that they were out of sight. In 14 cases of adenoma in which bronchoscopy was done and operation performed by Dr. Overholt[1] from 1943 to 1946, the adenoma was invisible in just 1. Also against an adenoma is the fact that the patient had no bleeding. An adenoma is very prone to bleed, and bouts of hemoptysis are a usual story. The clinical course otherwise seems to fit adenoma rather well — the age, the fact that he had had two episodes of pneumonitis in roughly the same place, and the fact that the pneumonitis did not heal in the first instance at least for thirty or forty days with extensive antibiotic therapy. It is interesting that characteristically the pneumonia in adenoma cases does heal after a period and that there are long periods of well-being in between attacks. The bullous emphysema could result from a sort of ball-valve effect created by the adenoma and the rapid emptying of the cavities, and filling up again could occur on the same basis. After the pneumonia healed there was little more than emphysema in addition to collapse. I feel on very shaky ground in clinging to a diagnosis of adenoma but I am obsessed with that idea for the moment. I think he had a small bronchial adenoma that may have arisen in one of the smaller bronchi with infection behind it and with a cystic bronchiectasis and possibly deterioration of the lung tissue to form cysts.

It is interesting that he was allowed to go home for a month before surgery was undertaken. I suppose the surgeons wanted to allow all the pneumonia to heal so that they would have to sacrifice as little lung tissue as possible when surgery was finally done.

A PHYSICIAN: Was this possibly a congenital cystic disease of the lungs?

DR. PIER: The patient had been so very well for the fifteen years that I would think it was unlikely.

CLINICAL DIAGNOSIS

Congenital cystic disease.

DR. PIER'S DIAGNOSES

Bronchial adenoma.
Bronchiectasis.

ANATOMICAL DIAGNOSIS

Syndrome of "lower accessory pulmonary artery, with intralobular sequestration of lung."

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: This patient presented a very unusual condition, which the thoracic surgeons, however, are beginning to see in significant numbers. The specimen was studied with great care by Dr. Mantz. I am going to ask him to describe it.

DR. FRANZ A. MANTZ: The specimen received consisted of the lower lobe of a right lung and presented a number of unusual abnormalities. The superior segment appeared somewhat collapsed, and the overlying pleura was discolored and roughened by numerous fibrous tags. At the costophrenic angle in the midposterior aspect there was the stump of a large aberrant artery, which entered the lung substance through a cleft-like dehiscence in the surface. The operative report stated that the vessel originated from the aorta. Conspicuous over the posterolateral aspect was an irregular longitudinal fissure, which roughly demarcated the posterior and superior segments. The substance of the posterior basal segment was somewhat firm to palpation, appearing slightly collapsed and mildly fibrous. Several small cysts were palpable here and two larger collapsed cysts were evident in the superior segment. Hilar dissection showed all major air passages to be present in normal number and relation.

The lower-lobe branch of the right pulmonary artery had been sectioned beyond its early ramification so that the vessels supplying the superior segment and median basal segments were isolated at the hilus while a common trunk remained supplying the arteries to the remaining three basal segments.

When the aberrant artery was injected with red latex solution, filling of the superior segmental artery and the artery to the anterior lateral and posterior basal segments occurred. The artery to the medial basal segment, having no connection with the latter trunk, did not fill. Dissection upward showed the aberrant artery to divide immediately into three channels distributed throughout the posterior basal segment, one of which extended upward to penetrate the superior segment. Throughout their course these vessels ramified extensively into tiny arteriolar twigs supplying the thin, smooth

membranous walls of large and small cysts widely dispersed throughout the substance of the two segments.

Dissection along the course of the superior, subsuperior and posterior basal segmental arteries showed similar ramification to the walls of the cysts at which site the dual circulation conjoined and freely interchanged. Although the arteries to the anterior and lateral basal segments were filled with latex, no cysts were found in these regions, and no branches from the aberrant vessel penetrated the segments. It must be assumed, therefore, that filling occurred in a retrograde fashion from the common trunk supplying all three segments. The fact that no latex was found in the artery to the medial basal segment that had been ligated beyond its origin tends to confirm this supposition.

No accessory or aberrant veins were noted. By injecting the vein draining the basal segments with blue latex solution we could demonstrate rich venous drainage through normal channels within the walls of the cysts just described.

The cysts, which were confined to the posterior basal and superior segments, varied from 5 mm. to 3 cm. in diameter, and all showed thin epithelial linings. Some were filled with thick mucopurulent material, but the majority contained scant amounts of clear fluid. Occasional cysts were multilocular, suggesting a branching tendency. All were surrounded by relatively normal parenchyma, and not a single instance of bronchial communication was demonstrated. When examined microscopically the cyst walls were densely fibrous. No cartilage, muscle or glands were seen, but the lining was invariably composed of bronchial epithelium. The surrounding pulmonary parenchyma displayed mild atelectasis, with foci of organized pneumonia, but was little altered otherwise.

The diagnoses in anatomical terms are congenital bronchogenic polycystic disease of the right lower lobe with recurrent infection, chronic focal organized pneumonitis and anomalous artery from the aorta to the left lower lobe.

The association of the anomalous artery with cyst formation, however, seems more than fortuitous and invites further consideration. Bruwer and his associates[2] at the Mayo Clinic, who have recently reviewed the literature, have found at least 26 similar surgical cases reported to which they have added 5 of their own. The commonest symptoms have been those of recurrent or intermittent pulmonary infection, and the commonest age at the time of onset has been under twenty years. Cursory review of the records of this laboratory indicates that at least 2 cases have occurred here in the past.

To explain the development of the abnormal artery one need only recall that the lung is derived as a branched budding from the primitive foregut. The latter structure is richly supplied by a plexus of anastomosing vessels arising from the dorsal aorta. In their earliest phase these arteries likewise supply the budding pulmonary anlage. As the pulmonary artery develops from the sixth branchial arch, however, it joins with the developing lung taking over the pulmonary circulation, following which the original blood supply derived from the aorta normally atrophies and disappears. When failure of atrophy occurs anomalous vessels such as that discussed here are left.

The bronchogenic cysts with their anomalous blood supply are less easily explained. Three theories predominate in the literature. The first of these was propounded by Eppinger,[3] who hypothesized the presence of accessory lung tissue isolated within the pulmonary substance. A second concept is that of fractionation of the developing lung produced by deepening of interlobar fissures and amputation by the developing aortic arch or by embryonic adhesions, thus separating twigs of bronchi and isolating them from their normal continuity. Recently, Pryce,[4] in England, who has studied 8 cases, has developed a concept that is more widely accepted in current literature. He has concluded that the persistent artery from the aorta to the pulmonary anlage attaches itself to rounded bulbs of budding bronchi and there enters into competition with the pulmonary artery. As the embryo grows and straightens and as the lung shifts into a more cephalad position, the attached bulb is gradually torn away and isolated, producing rests from which cysts may develop. He believes that the two abnormalities are related, producing an abnormal developmental entity that he classifies as "lower accessory pulmonary artery with intralobar sequestration of the lung."

DR. MALLORY: Have you any comments from the surgical point of view, Dr. Scannell?

DR. GORDON A. SCANNELL: I have not anything to add. Dr. Mantz has worked up the anatomical aspects of it very well. It is a most interesting anomaly.

DR. MALLORY: This is a well defined syndrome in which multiple cysts in the lungs are associated with an aberrant artery from the aorta to the lower lobe. It is apparently very characteristic, as in this case, to see recurrent episodes of pulmonary infection eventually requiring resection.

A PHYSICIAN: Is the patient doing well?

DR. MALLORY: I believe the patient was completely relieved.

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CASE 36362

Presentation of Case

A seventy-year-old man was admitted to the hospital because of abdominal pain and vomiting.

Eight months prior to admission the patient first noted generalized aching abdominal discomfort not related to meals. Two weeks before admission the pain increased slightly in severity. Four days prior to entry he began to vomit several times daily. Initially, the vomitus contained only food, but soon it contained yellow and brown fluid. Simultaneously with the onset of the vomiting the generalized abdominal pain became more severe. For the three days prior to admission the patient produced virtually no urine at all. There was no antecedent history of urinary difficulty. In the twenty-four hours prior to admission no gas had been passed by rectum.

On physical examination the patient was slightly disoriented. The skin and mucous membranes were dry. The abdomen was slightly distended and was tender over its entirety. There was slight rebound tenderness. There were no masses.

The temperature was 99°F., the pulse 100, and the respirations 20. The blood pressure was 185 systolic, 105 diastolic.

Examination of the blood disclosed a hemoglobin of 13.5 gm. and a white-cell count of 16,300, with 87 per cent neutrophils. The amount of urine obtained was insufficient for determination of the specific gravity; it gave a + to ++ test for albumin and contained no sugar or bile. The urinary sediment contained 10 to 20 red blood cells per high-power field after a catheter had been in place for eight hours. The nonprotein nitrogen was 127 mg., and the total protein 7.2 gm. per 100 cc., and the carbon dioxide 18.0 milliequiv., the chloride 100 milliequiv., the sodium 132.0 milliequiv., and the potassium 7.4 milliequiv. per liter; the prothrombin time was 25 seconds (normal, 17 seconds). The guaiac test on the stool was ++. A plain film of the abdomen was reported as showing no distention of the small or large intestine.

Shortly after admission the patient passed gas by rectum. A Miller–Abbott tube was passed, which stayed in the fundus and partially controlled the vomiting. Three thousand cubic centimeters of fluid was given on the first hospital day, with a urinary output of 20 cc. On the second hospital day the patient's condition remained about the same. The calcium was 8.0 mg., the phosphorus 6.5 mg., the alkaline phosphatase 6.9 units and the nonprotein nitrogen 150 mg. per 100 cc. The fluid intake was 2000 cc. on the second day, with virtually no output. On the third day fluid intake was 1200 cc., with no output. The nonprotein nitrogen was 170 mg. per 100 cc. A retrograde pyelogram was attempted, but neither ureter could be catheterized. On the fourth hospital day while being prepared for a run on the artificial kidney the patient died.

Differential Diagnosis

Dr. Earle M. Chapman*: It seems clear that this man died because he was in bilateral renal failure, and it is up to me to make the diagnosis despite the paucity of evidence in the history pointing to the mechanism of the renal failure. First I should like to point out the similarity of the history of the disease to that of intestinal obstruction. From the history he appeared to have lower bowel obstruction. However, subsequent evidence certainly was against it; films of the abdomen were normal, and he passed gas. These are also the symptoms of renal failure, and uremia has simulated intestinal obstruction so I think I will exclude that clinical possibility.

With the evidence at hand, I shall have to clutch at straws to predict what type of renal failure Dr. Mallory will reveal to us. One thinks of an acute glomerulonephritis, but there was nothing in the clinical history to suggest this. The only story is that, eight months prior to admission, the patient noted generalized abdominal discomfort. Could it have been an acute arteriosclerotic Bright's disease? With Bright's disease there should have been a longer history of frequency of urination, especially at night, and other symptoms that would have pointed to renal damage.

Next one has to consider an intravascular disorder affecting both kidneys, such as thrombosis within the arterioles, arteries or even the veins. The findings might be explained on the basis of a thrombosis and infarction of the kidneys. I believe the whole kidney was involved because the evidence clinically was consistent with total renal failure, not with that variety that has been described as the tubular type or lower-nephron nephrosis. As both blood potassium and phosphatase were elevated I believe the calcium had fallen as a secondary phenomenon, and I do not think I can call it secondary to hyperparathyroidism but perhaps the autopsy will show the parathyroids to be larger than normal.

Another possibility in an elderly man is that tumor was present. If so, was it extrinsic or intrinsic to the genitourinary tract? Again, I have no clue. The fact that the surgeon was unable to take the retrograde pyelogram makes me suspect that the ureters were obstructed by tumor — an invasive tumor that may have spread from the bladder or tumor growing along the course of the ureters before the bladder was reached, causing the obstruction. Since the surgeon apparently could not insert a catheter into the ureteral orifices, one has to think of tumor in this area. Because of the elevated phosphatase, which indicates some disturbance of the bone marrow, I thought of

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metastatic tumor in the marrow or a rather rare type of tumor, perhaps myeloma. This might have been multiple myeloma, with myeloma kidneys.

One has to think of other diseases such as amyloid kidney, but again there is no evidence at all except the elevated phosphatase that makes me suspect that there might be some widespread systemic disease. That is as far as I can go.

I am certain the patient had renal failure and not intestinal obstruction. It is going to be up to Dr. Mallory to tell us what type of disease was found obstructing the kidneys.

A PHYSICIAN: What did the x-ray films of the kidney show?

DR. STANLEY M. WYMAN: There is some filling of the right urinary passages at the time the retrograde pyelogram was attempted. The kidney outlines are not well seen, but I think they are probably within normal limits in size and shape. I cannot make any comment about the bladder.

DR. CHAPMAN: I did not realize that any dye reached the right kidney.

DR. TRACY B. MALLORY: The catheter passed up the ureter only a short distance.

DR. CHAPMAN: There is no evidence of calcification such as is seen in renal rickets.

DR. WYMAN: No. The bones are very osteoporotic.

DR. CHAPMAN: Are they any more osteoporotic than they would be in a man of seventy years?

DR. WYMAN: I think one would have to consider bone-marrow disease in this patient.

DR. CHAPMAN: One would think of myeloma or bone-marrow disease.

DR. ALFRED E. KRANES: The phosphatase is not elevated in myeloma. It is usually fairly normal. I wonder about the abdominal pain that continued for eight months. Do you think it was due to uremia all that time? Did that lead you to the diagnosis of tumor with ureteral obstruction?

DR. CHAPMAN: I thought the pain in the abdomen fitted with a thrombotic process — that the patient had either thrombosis or tumor. I did not think that he had chronic uremia. I think he had an underlying disease for some time and that the uremia was of recent origin — that it came on within the last two weeks prior to admission, and was based on the ureteral obstruction demonstrated. I do not think the pain and discomfort would be interpreted as being due to renal failure.

DR. JAMES H. CURRENS: Is anything known about the urinary output preceding the terminal illness?

DR. MALLORY: As far as we know, it was perfectly normal. The oliguria was quite sudden and terminal.

A PHYSICIAN: Do you see anything unusual about the pelvis of the kidney to suggest obstruction?

DR. WYMAN: From this incomplete examination I cannot see any evidence for obstruction.

A PHYSICIAN: Can you exclude intussusception, with rupture through the intussception, so that he eventually passed gas?

DR. WYMAN: There is nothing to suggest intestinal obstruction on these films.

CLINICAL DIAGNOSES

Chronic glomerulonephritis, with uremia.
Generalized arteriosclerosis.

DR. CHAPMAN'S DIAGNOSES

Bilateral renal failure.
Invasive tumor, with ureteral obstruction, ? type and source.

ANATOMICAL DIAGNOSIS

Carcinoma of stomach, with retroperitoneal metastases and infiltration of ureters.
(*Uremia.*)

PATHOLOGICAL DISCUSSION

DR. MALLORY: This man was brought to the hospital by his wife, who provided us with the diagnosis. She said, "He has cancer of the stomach," and she was quite right but nobody paid any attention to her. A large ulcerating lesion was found on the lesser curvature, with edema of the stomach walls extending in both directions from it. The tumor had spread to the pancreas, around which many metastatic lymph nodes were found. It also extended to the retroperitoneal nodes, and a diffuse tumor infiltration had occurred about the base of the bladder, involving both of the seminal vesicles and both ureters. Tumor extended up and down both ureters for a considerable distance, without producing any point of complete occlusion. It was very difficult to pass a probe from the ureter through the orifice into the bladder, but it was possible to get one through. I think unquestionably there was a high degree of obstruction although it was not absolutely complete as was proved by the fact that a little dye did get past on one side. The kidneys were completely normal. There was no hydronephrosis on either side. That is, of course, the rule when ureteral obstruction is very acute and complete. The patients with long-standing incomplete obstruction develop a hydronephrosis.

DR. CHAPMAN: May I ask on what criteria the wife made the diagnosis of carcinoma of the stomach?

DR. MALLORY: I do not believe she explained the reason.

DR. CHAPMAN: I certainly doff my hat to the lady.

The New England Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
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MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

A STUDY OF PUBLIC MEDICAL CARE

THE present issue of the *Journal* contains a careful exposition by Dr. Franz Goldmann, associate professor of medical care at the Harvard School of Public Health, of public medical care as it exists today in Great Britain and the Scandinavian countries. Dr. Goldmann, who has recently visited the four countries under consideration on a travel grant from the Rockefeller Foundation, finds nothing static about the development of medical care or the methods by which it is distributed to its recipients.

The systems in vogue at present, he reports, have resulted from long experimentation and are still under revision; he further finds that the people in these countries unqualifiedly endorse the establishment of inclusive systems of medical care as well as the principles of national responsibility and of government action to attain comprehensive medical care for all persons. Medical care programs are necessary for all, they believe, if all are to have equal opportunities to live satisfying and useful lives, and "to construct societies where men will be both free and happy and, ultimately, to attain social as well as political democracy."

The plans differ in various ways. All include public medical care, which in Norway and Denmark is combined with compulsory, and in Sweden with voluntary health insurance. In Sweden, however, it is subsidized by the Government out of general tax funds. In Great Britain, the country that has most recently extended its system, the basic characteristics are those of public medical care and not of compulsory sickness insurance.

A disquieting feature in at least Great Britain's system of public medical care seems to be a loss of prestige of the general practitioner and a glorification of the specialist to an undesirable degree.

In an attempt to evaluate properly public medical care — a most difficult task when practically all viewpoints are factional and most opinions are based on prejudice — it must be taken into consideration that the four countries discussed are perhaps the select group of all the democratic nations in which the temperament of the people is best suited to the initial success of these social experiments. It must also be discounted that New Zealand and Australia have taken turns to the right, and that England's Socialist Government has recently found its seat the most uneasy of its career.

How well the people of these countries like the type and quality of their medical care may still be open to question, despite Dr. Goldmann's assurance of their devotion to it. Quite different reports have been brought from England by Mr. Ewing and Mr. Stassen, for instance. What will be the eventual lot of a people that abandons itself to the reckless comfort of complete security — a delusion if there ever was one? These are questions that must be answered, with the suspicion in mind that the eventual outcome of parasitism is loss of function of the parasite.

The decisions that this country makes must be based on the information derived from such careful observations as Dr. Goldmann's, reliably reported and accurately interpreted.

THE NONMILITARY HOSPITAL IN TIME OF WAR

Two letters to the editor published elsewhere in this issue of the *Journal* view the hospital problems of a large and important city, especially in terms of emergency service, from somewhat different angles.

Bradford, in discussing elementary preparations alone, indicates those that must be made to care for even a limited emergency. This, which might come with a state of only localized war, as exists at present, could include large-scale sabotage and local disaster and would require preparation for certain specific problems having to do with the operation of hospitals under difficult conditions.

These conditions might include the sudden necessity of caring for a great number of casualties, the loss of electric power and the crippling of communications, the depletion of supplies, the redistribution of many patients to more remote hospitals, and unusual fire risks. They would necessitate the training of staffs to deal with special emergencies, including, in anticipation of a major catastrophe, the treatment of patients suffering from atomic radiation.

In addition to elementary preparations, long-range planning, in Bradford's opinion, calls for the affiliation of every metropolitan hospital with a peripheral hospital, which would be equipped for emergency use and could be staffed or partly staffed from the personnel of the urban institution. Unfortunately Boston, in its present situation, is confronted with a dearth of such peripheral hospitals 15 to 30 miles outside the city. Even yet the country is not fully appreciative of the often-expressed warning that the threat of atomic warfare can be adequately met only by a decentralization of vital resources.

The letter from Lund, on the other hand, takes issue with the opinion expressed editorially in the *Journal* on August 3 that it is folly to be building a new Veterans Administration hospital within the city limits of Boston. This location, he points out, was carefully planned to make the hospital available to the highest quality of staff — certainly a laudable objective, and one intended to correct a common mistake of the Veterans Administration in the past, in having located hospitals in more or less remote areas.

In his final statement, however, Dr. Lund reflects what may be considered as the logical attitude on this point:

> . . . that one should not jump to place Veterans Administration hospitals in far distant places, but should try to find the optimum location balancing danger of bombing close to the center of a city against decreased efficiency at a distance from the city.

The location of the hospital under discussion would seem hardly to represent this conservative middle distance between vulnerability to attack and inaccessible remoteness.

MILK AND MAMMARY CANCER

An agent present in their mothers' milk has been shown to be largely the cause of cancer of the breast in mice of certain inbred strains. In them this form of cancer "can be for all practical purposes exterminated by the simple measure of foster nursing of one single generation." When Bittner announced this discovery, hopes were high that here was an entering wedge into the elucidation of carcinogenesis in human beings.

In this issue of the *Journal* Berner summarizes the investigations concerning this agent and discusses their implications regarding the prevention of mammary cancer in women. No milk factor has been demonstrated for breast cancer in man. There is no evidence that the human situation is analogous to that in mice. Nevertheless, Berner is of the opinion, shared by others, that women with family histories of breast tumors should avoid giving any of their milk to their children. This would be one step, involving little sacrifice, in the application of the theory that mammary cancer may be transmitted via the milk of the nursing mother.

While Berner was writing his review, Horne was carrying on his investigation, also reported in this issue. He determined with reasonable certainty that 9 of 88 women with cancer of the breast had never received any human milk. According to this finding, withholding of human milk from a large number of female babies would not eliminate can-

cer of the breast in that group. Whether or not such an experiment might reduce the incidence of breast cancer remains to be discovered. In the meantime, early diagnosis is still the only way of reducing the mortality from this disease.

APPOINTMENT OF DR. HAM

THE removal of Massachusetts physicians to the lands beyond the Mississippi has not yet reached the proportions of an exodus, but it is with mixed feelings that the *Journal* announces that still another doctor has recently taken his way to the Midwest. Last year Dr. Alan R. Moritz left Boston for Cleveland,[1] and only recently it was announced that Drs. Carroll B. Larson and Charles H. Burnett had accepted positions in Iowa and Texas.[2] Now comes word that Dr. Thomas Hale Ham, assistant professor of medicine at Harvard Medical School and associate director of the Thorndike Memorial Laboratory, Boston City Hospital, has been appointed professor of medicine and chairman of the committee on medical education at Western Reserve University School of Medicine in Cleveland, Ohio. The appointment is Boston's loss and Cleveland's gain, but Dr. Ham is assured of wishes for the greatest success in his new position and of a warm welcome when he visits the scene of his early accomplishments.

Both Dr. Ham and Western Reserve University are congratulated — the former on the honor of occupying the important post of professor of medicine and the latter on acquiring the services of a physician who has distinguished himself in the positions he has held in Boston.

REFERENCES

1. Editorial. Dr. Alan R. Moritz. *New Eng. J. Med.* **241**:675, 1949.
2. Editorial. Westward ho! *New Eng. J. Med.* **243**:63, 1950.

On Friday last, 30th ult., pursuant to the executive warrant, Dr. John W. Webster suffered the extreme penalty of the law for the murder of Dr. George Parkman in November last . . . With respect to the justness of the sentence now executed, it is not at this time our purpose to speak; but as our views on the death penalty differ from those of the majority, we may be allowed to say that we hope it will be the last time there will be cause, in our commonwealth, to carry into execution such a dreadful sentence.

Boston M. & S. J., *Sept. 4, 1850*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

COTTLE — Louis A. Cottle, M.D., of Worcester, died on June 21. He was in his seventy-seventh year.

Dr. Cottle received his degree from University of Pennsylvania School of Medicine in 1899. He was president of the corporation of Worcester Emergency Hospital and formerly staff physician at Fairlawn Hospital.

His widow survives.

DEVLIN — Peter C. Devlin, M.D., of Lynn, died on July 25. He was in his seventy-third year.

Dr. Devlin received his degree from Baltimore Medical College in 1902. He was a fellow of the American Medical Association.

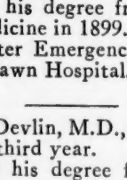
His widow, a daughter, two sisters and two brothers survive.

MEINHARDT — Charles Meinhardt, M.D., of Malden, died on May 13. He was in his fifty-first year.

Dr. Meinhardt received his degree from College of Physicians and Surgeons, Boston, in 1935.

A sister and two brothers survive.

BOSTON MEDICAL LIBRARY



RECENT IMPORTANT ACCESSIONS

The Library from time to time has opportunity to acquire for its historical collections items of exceptional interest. Some important books and plates purchased from special restricted funds have recently been added.

Especially noteworthy is: the *Libro de medicina llamado compendio de la salud humana*, a Spanish version of the *Fasiculus medicinae* of Johannes de Ketham (Seville, 1517). Two chapters have been added: *Oratio devotissima ad Sanctum Sebastianum: ad impetraroum salutem contra pestem;* and *Tractado dela arte de phisonomia.* The Ketham work is illustrated with the urine chart and five of the large cuts found in the Latin editions. The volume also contains *Tractado llamado menor dano de medicine*, by Alfonso Chirino (Seville, 1526). The Sebastian tract on the pest is unusual, and the Ketham is very scarce and important. The Library has two earlier editions of Chirino (Seville, 1506, and Acabose, 1506). The book is from the Arthur Abegglen Library, sold in New York City on March 16, 1950.

Two other items are of outstanding anatomic interest. One is Leone Giambattista Carcano's *Anatomici libri II. In quorum altero de cordis vasorum in*

foetu unione pertractatur, . . . In altero de musculus palpebrarum atque oculorum motibus deservientibus disseritur (Pavia, 1574). Carcano was a pupil of Fallopio and taught anatomy at Pavia in the sixteenth century. The first tract contains his researches on the vessels of the heart in the fetus, describing the oval foramen. In the second he describes the straight and oblique muscles of the eye. The part on the eye discusses the work of Vesalius and corrects his mistakes, mentioning him by name on nearly every page. The little volume is of outstanding rarity and also of great importance for the history of early anatomy. It was not mentioned by Dr. Cushing, the collector and bibliographer of Vesalius.

The second item is a series of twenty folio plates drawn by Antonio Cattani of Bologna, in the natural size of the subject, and engraved on copper, printed "presso Volpe" and "presso l'autore," 1778–1779, presumably at Bologna. All plates are signed by Cattani, and are numbered one to twenty. They are unbound and in the original state as issued, and are fine impressions from the copper plates. They represent the osteology and myology of the head, hand and foot. The plates were issued separately, probably for the use of students at Bologna. On plate No. 13, dated November 16, 1778, there is a note stating that separate plates will be issued every forty days. The series is of extraordinary rarity, only one other complete set being recorded at the present time. It is not noted in any of the standard bibliographies, including Medici's history of the School of Anatomy at Bologna during the eighteenth century. Single plates may have survived the use of students, but their whereabouts are unknown. The second existing set is in the Vittorio Putti collection in the Istituto Rizzoli in Bologna. The set acquired by Putti presents a bibliographic problem. It is bound in a large folio volume and has a title page dated 1780 reading as follows: *Osteografia e miografia della teste, mani, e piedi del corpo umano in misura naturale con e catalogo de nomi propri di tutte le sui parti* (Bologna, presso Antonio Cattani, e Antonio Nerozzi, 1780). It is probable that this title page was issued separately on the completion of the series for the convenience of owners of sets and for binding purposes. From the artistic and technical points of view, the plates are magnificent. They were purchased for the John Warren collection on anatomy.

CORRESPONDENCE

METROPOLITAN HOSPITALS IN TIMES OF WAR

To the Editor: May I call attention to one of the most important aspects of civilian defense that I am sure deserves further discussion? The metropolitan hospitals play such vital parts in our communities today that we must plan every means to safeguard them in case of attack. In a study of various measures for protection, it is wise to differentiate the stages of danger that confront us. While peace still remains — or we should say, while war continues to be localized — the risk of attack may be ever present; but it cannot yet be said to be imminent. There may, however, come a time when the outbreak of wholesale warfare seems both certain and closely impending. Again, an unexpected, sneak attack, when bombs actually fall, may occur. We are at present in the first of these categories of danger, and we must prepare ourselves for the other two.

Elementary preparations are obviously the first to undertake. These will consist in alerting the hospitals to the needs of immediate action for what may be called a limited emergency. Without presupposing a major bombing attack or the possibilities of large-scale sabotage or local disaster, problems such as the following would be raised:

Great numbers of casualties might suddenly be brought to the hospital. Would emergency facilities make it possible to handle the overflow? Could the wounded be sorted, treated for shock, operated, nursed in beds and evacuated?

Power might be cut off, depriving the buildings of light, heat or elevator service. Could top-floor operating rooms be used? Would surgical sterilizers and autoclaves function? Could the wards be kept warm?

Has provision been made for assembling the staff in case telephone communication fails? It must be remembered that the surgical staff could not serve effectively without nurses, technicians, attendants and nonmedical personnel.

In addition to traumatic wounds, there are likely to be unusual numbers of burn cases, of fractures and possibly of head injuries. Will specialists in these fields be readily available? Is the hospital equipment adequate for a flood of such cases?

Would surgical supplies hold out, and would the hospital's reserve stock meet the demands of double or triple its usual bed capacity?

Two of the most urgently needed supplies that would be called for in great quantity would be chemotherapeutic drugs and blood or plasma. Could they be provided promptly?

What arrangements are available to redistribute an overload of patients to more remote hospitals?

Has the hospital staff been trained regarding atomic radiation, and has a satisfactory routine procedure been adopted in case of such an emergency?

Unusual fire risks might occur in or near the hospital. Has every precaution been taken to minimize these risks?

How would identification and disposal of large numbers of dead bodies be handled?

It is not worth while for any single person to attempt a general plan in answer to these questions. Better preparations will be made if each hospital staff considers them individually and draws up its own standard operating procedure with these problems in view, and with others that may come to mind. From comparison of many independent solutions to these problems as a whole, an over-all, routine standard may grow to be accepted. The present emergency seems acute enough for every hospital to give immediate attention to these matters, and for solutions to be worked out within the next month.

The second great problem is to work out a policy for the large metropolitan hospitals in case the present danger increases to the stage of an acute and immediate threat. Observers may disagree about the possibilities, but we cannot escape the fact that peace in the future seems extremely uncertain. To ignore this menace would be to hide from reality.

It is clear that any atomic burst over the center of a city will destroy all nearby hospitals and will render the more remotely neighboring hospitals unserviceable. Thus, against a sudden, sneak attack, there is no defense. When this is known in advance, it becomes especially important to minimize the hazard as much as possible. A similar problem on a smaller scale was faced by the British at the time of the *Blitz*. It was met by evacuation of all long-term patients from municipal hospitals to peripheral institutions, which were staffed by the same doctors as in the corresponding hospital in the city. If an imminent emergency develops here, this sort of evacuation would be a wise plan to adopt, but it cannot be carried out unless we begin now to provide peripheral institutions for this service. Once these are ready, the following steps can be taken as soon as acute danger appears.

Each of the larger hospitals in the city can affiliate itself with one of the peripheral hospitals, either taking over an institution completely and staffing it, or taking over a section of some suburban hospital in association with the existing staff. Such hospitals must be equipped and made serviceable in advance for their emergency use, not only for routine but also for high-grade specialization if this should be necessary.

All patients requiring more than ten days' convalescence, and all confinement cases can and should be evacuated to the peripheral hospitals. Elective surgery should be stopped altogether or postponed until the acute emergency subsides.

Metropolitan hospitals should continue to treat acute, short-term cases despite the emergency, and should maintain outpatient departments on a limited scale.

A complete change-over such as has been suggested would create tremendous loss of defense time if practiced in every city in the state. It would be more advisable that evacuation of patients should be limited to cities designated as primary target areas. Cities of less strategic importance should prepare for possible evacuation, but should not rush into it until ordered by the civilian defense agency. It must be strongly emphasized that evacuation is an essential step for every metropolitan hospital in a primary target area, and that preparations for evacuation are essential in every secondary target area. Without a plan of this sort, no intelligent effort toward medical defense can be said to exist.

An objection may be raised that peripheral institutions suitable for hospital use are not now available on any scale that will meet the need. This is the very reason that it is necessary to begin energetic plans at once for organizing or building such institutions. At whatever cost, available beds must be provided 15 to 30 miles outside the city, and arrangements must be made for staffing and servicing these hospitals in affiliation with corresponding municipal hospitals. The present threat of total war seems acute enough to justify setting a time-limit for completing such preparations within the next two years.

The third problem is to prepare plans for the metropolitan hospitals in case of a sudden, sneak attack. Study will show that no organizational preparation or defense is available to meet this danger, and therefore it seems that planning is useless. "Things without all remedy should be without regard." If a hospital is only partially damaged, prompt evacuation will become its immediate problem. This would have to be left to the state ambulance service, which is now being considered for emergency planning.

Certainly, all hospitals in a city are not likely to be totally destroyed — some may be obliterated; some will be badly wrecked; and some will be only lightly damaged. The latter could be used as dressing stations for casualties during the emergency. Since the entire surviving populations would continue instinctively to think of hospitals as places of refuge, it would be wise to maintain even the wrecked buildings for first-aid and clearance purposes. These, however, are the only useful purposes they could serve in the event of proximity bombing, and beyond this, it is useless to plan.

In summary, the present emergency makes it advisable for every metropolitan hospital to study and prepare a standard operating procedure for handling large numbers of casualties in case of a limited attack. These plans should be made ready as soon as possible. Practice alerts, to test them out, might be worth recommending.

Plans should be prepared for affiliation of metropolitan hospitals with corresponding peripheral institutions capable of accommodating their patients. Energetic steps should be taken to complete these plans within the next few months.

In case of imminent attack, cities designated as primary targets should evacuate all except short-term surgical or emergency cases to their peripheral affiliates. Metropolitan hospitals should continue to treat short-term emergency surgery or obstetrics, and should continue limited outpatient service.

In case of direct bombing, the surviving metropolitan hospitals should function as casualty-clearing stations.

CHARLES H. BRADFORD, M.D.

Boston, Massachusetts

LOCATION OF VETERANS ADMINISTRATION HOSPITALS

To the Editor: The editorial "Urgent Business" in the August 3 issue of the *Journal* is a splendid plea to plan to merge the Government medical services with civilian medical services in case of an all-out war in which heavy bombing of American cities may occur. However, in the editorial the following statement is quite a harsh attack on the people responsible for policy and administration of the Veterans Administration: "The obvious disadvantage of having the important available hospitals concentrated in the target areas of cities is apparent, and one can but be appalled at the folly of adding to this concentration by building a new Veterans Administration hospital inside the city limits of Boston."

Actually, the placement of this new hospital and many other similar actual and proposed new hospitals in other cities resulted from careful planning of the Veterans Administration in order to make possible the highest possible quality of staff. Bitter experience has shown the Administration that locations well away from medical centers made it impossible to maintain good medical and surgical services. A quotation to this point is to be found in the article by the late Dr. Roy R. Kracke, entitled "Medical Care of the Veteran," in the *Journal of the American Medical Association* (**143**: 1326, 1950):

> Veterans' hospitals should be located in those areas of the country where the staffing of the institutions will present the least difficulty. Therefore it is necessary that the institutions be located in urban areas where there are large concentrations of physicians and other medical personnel. One of the great mistakes of the Veterans Administration in the past has been the location of institutions in more or less remote areas. This resulted in staffing difficulties to the point where there was serious disintegration in the program of medical care.
>
> Many of the hospitals are being built as teaching hospitals, around medical schools wherever possible, and nearly every medical school in the United States is directly or indirectly concerned in the medical care of the veteran. Great pressures are always brought on the Veterans Administration to place hospitals in the undesirable locations. For the most part these pressures have been successfully resisted, although there are rare instances, particularly in the previously established ten-year building program, in which an institution has been erected in an undesirable location.

In view of such considerations one should not jump to place Veterans Administration hospitals in far distant places, but should try to find the optimum location balancing danger of bombing close to the center of a city against decreased efficiency at a distance from the city.

CHARLES C. LUND, M.D.

Boston, Massachusetts

NOTICES

MASSACHUSETTS SOCIETY OF ANESTHESIOLOGY

The Massachusetts Society of Anesthesiology will present its annual Post Graduate course on the first Saturday of each month from October, 1950, through February, 1951. Information may be obtained from M. Gene Black, M.D., 575 Beech Street, Holyoke, Massachusetts.

CONNECTICUT AND YALE CLINICAL CONGRESS

The twenty-fifth Clinical Congress of the Connecticut State Medical Society and the Yale University School of Medicine will be held at the Grace–New Haven Community Hospital and the Yale School of Medicine on September 12, 13 and 14. The morning sessions will take place in the auditorium of the Yale Law School.

(*Notices concluded on page xiii*)

NOTICES (*Concluded from page 394*)

MICROFILM VOLUMES OF *JOURNAL* TO BE MADE AVAILABLE

The *Journal*, in order to help solve the storage problem with which all libraries are confronted, has entered into an agreement with University Microfilms, of Ann Arbor, Michigan, to make its issues available in microfilm form.

The microfilm process makes it possible to distribute volumes of the *Journal* in single rolls in editions of 30 or more, at a cost approximately equal to that of binding the volumes. The saving in storage space is obvious.

Sales of microfilm volumes, which are furnished as positive film on metal reels, are restricted to regular subscribers to the *Journal*, and film copy is only distributed at the end of the volume period.

Inquiries concerning purchase should be made to University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

VAN METER PRIZE AWARD

The American Goiter Association again offers the Van Meter Prize Award of $300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association, which will be held in Columbus, Ohio, May 24, 25 and 26, 1951, provided essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length and must be presented in English; a typewritten, double-spaced copy in duplicate must be sent to the corresponding secretary, Dr. George C. Shivers, 100 East Saint Vrain Street, Colorado Springs, Colorado, not later than March 1, 1951. The committee reviewing the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the annual *Proceedings* of the Association.

SOCIETY MEETINGS AND CONFERENCES

September 12–14. Connecticut and Yale Clinical Congress. Page 394.
September 14. Progress in the Management of Hand Injuries. Dr. Henry E. Marble. Pentucket Association of Physicians. 8:30 p. m. Haverhill.
September 18–27. International Congress of Psychiatry. Page 240, issue of August 10.
September 26–29. American Roentgen Ray Society. Page 240, issue of August 10.
September 27. American Medical Writers' Association. Page xi, issue of July 13.
September 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.
October 3. Massachusetts Academy of General Practice. Boston City Hospital and Hotel Kenmore.
October 6–May 11. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 324, issue of August 24.
October 12–14. American Association of Blood Banks. Page 428, issue of March 16.
October 14–19. American Academy of Pediatrics. Page 962, issue of June 15.
October 23–27. American College of Surgeons. Page xi, issue of June 29.
October 23–28. Medicomilitary Symposium for Officers of Fourth Naval District. Page 34, issue of July 6.
October 28. Massachusetts Association of Medical Technologists. Page 324, issue of August 24.
October 30–November 3. American Public Health Association. Page 240, issue of August 10.
October 31–November 3. International College of Surgeons. Page 170, issue of July 27.
November 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.
November 1. Hampshire District Medical Society. Page 170, issue of July 27.
November 5 and 6. American Society for the Study of Arteriosclerosis. Page 170, issue of July 27.

District Medical Society

HAMPSHIRE

November 1. 4:30 p.m. Northampton State Hospital.
January 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
March 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
May 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

Calendar of Boston District for the Week Beginning Thursday, September 14

Friday, September 15

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.
*1:30 p.m. Tumor Clinic. Out-Patient Department. Mount Auburn Hospital, Cambridge.

Monday, September 18

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

Tuesday, September 19

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

Wednesday, September 20

*12:00 m.–1:00 p.m. Grand Rounds. Amphitheater, Children's Hospital.

*Open to the medical profession.

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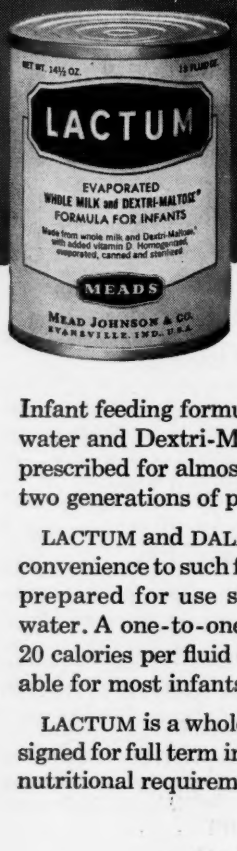

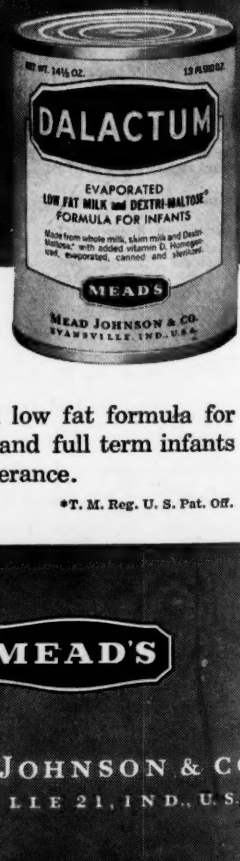

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